(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068743 A1

(51) International Patent Classification[7]: C07D 211/52, 211/14, 401/12, 409/12, 417/12, A61K 31/445, 31/4523, A61P 11/06, 19/02, 31/00

(21) International Application Number: PCT/SE03/00258

(22) International Filing Date: 17 February 2003 (17.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0200465-3 18 February 2002 (18.02.2002) SE
0202673-0 9 September 2002 (09.09.2002) SE

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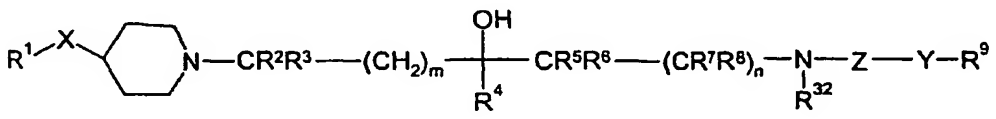
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CHEMICAL COMPOUNDS



(I)

(57) Abstract: The invention provides compounds of formula (I):[Chemical formula should be inserted here. Please see paper copy]wherein: X is CH_2, O, $S(O)_2$ or NR^{10}; Y is a bond, CH_2, NR^{35}, CH_2NH, $CH_2NHC(O)$, CH(OH), $CH(NHCOR^{33})$, $CH(NHSO_2R^{34})$, CH_2O or CH_2S; Z is C(O), or when Y is a bond Z can also be $S(O)_2$; R^1 is optionally substituted aryl,optionally substituted heterocyclyl or C_{4-6} cycloalkyl fused to a benzene ring; and R^2, R^3, R^4, R^5, R^6, R^7 and R^8, R^9, R^{10}, R^{32}, R^{33}, R^{34} and R^{35} are as defined herein;are modulators of chemokine (especially CCR3) activity (for use in, for example,treating asthma). The invention also provides a process for making 4-(3,4-dichlorophenoxy)piperidine, which is useful as an intermediate for making certain compounds of the invention.

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CHEMICAL COMPOUNDS

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents. The invention also provides a process for making 4-(3,4-dichlorophenoxy)piperidine, which is useful as an intermediate for making certain compounds of the invention.

Pharmaceutically active piperidine derivatives are disclosed in WO 01/62728, WO 01/62729 and WO 01/62757.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

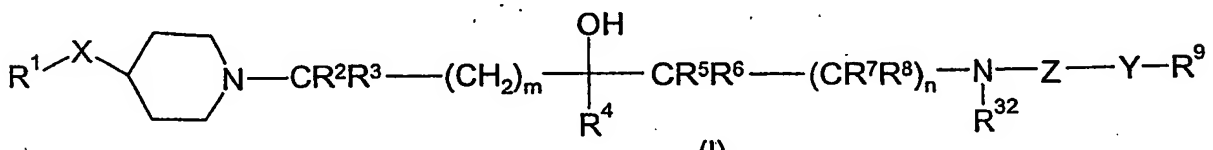
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes, but not neutrophils, such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxins and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of three main types, H1, H2 and H3. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, especially rhinitis and urticaria. Antagonists of H1 are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Viral infections are known to cause lung inflammation. It has been shown experimentally that the common cold increases mucosal output of eotaxin in the airways. Instillation of eotaxin into the nose can mimic some of the signs and symptoms of a common cold. (See, Greiff L *et al* Allergy (1999) 54(11) 1204-8 [Experimental common cold increase mucosal output of eotaxin in atopic individuals] and Kawaguchi M *et al* Int. Arch. Allergy Immunol. (2000) 122 S1 44 [Expression of eotaxin by normal airway epithelial cells after virus A infection].)

The present invention provides a compound of formula (I):



(I)

wherein:

X is CH_2, O, $S(O)_2$ or NR^{10};

Y is a bond, CH_2, NR^{35}, CH_2NH, $CH_2NHC(O)$, $CH(OH)$, $CH(NHC(O)R^{33})$, $CH(NHS(O)_2R^{34})$, CH_2O or CH_2S;

Z is C(O), or when Y is a bond Z can also be $S(O)_2$;

R^1 is optionally substituted aryl, optionally substituted heterocyclyl or C_{4-6} cycloalkyl fused to a benzene ring;

R^4 is hydrogen, C_{1-6} alkyl (optionally substituted by C_{3-6} cycloalkyl) or C_{3-6} cycloalkyl;

R^2, R^3, R^5, R^6, R^7 and R^8 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

m and n are, independently, 0 or 1;

R^9 is optionally substituted aryl or optionally substituted heterocyclyl;

R^{10}, R^{32} and R^{35} are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^{33} and R^{34} are C_{1-6} alkyl or C_{3-6} cycloalkyl;

wherein the foregoing aryl and heterocyclyl moieties are, where possible, optionally substituted by: halogen, cyano, nitro, hydroxy, oxo, $S(O)_kR^{12}$, $OC(O)NR^{13}R^{14}$, $NR^{15}R^{16}$, $NR^{17}C(O)R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, $S(O)_2NR^{22}R^{23}$, $NR^{24}S(O)_2R^{25}$, $C(O)NR^{26}R^{27}$, $C(O)R^{28}$, CO_2R^{29}, $NR^{30}CO_2R^{31}$, C_{1-6} alkyl (itself optionally mono-substituted by NHC(O)phenyl), C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{1-6} alkylthio, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, morpholinyl, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halogen, hydroxy, nitro, $S(O)_r(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

k and r are, independently, 0, 1 or 2;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27}, R^{29} and R^{30} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), C_{3-6} cycloalkyl, phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

alternatively $NR^{13}R^{14}$, $NR^{15}R^{16}$, $NR^{20}R^{21}$, $NR^{22}R^{23}$, $NR^{26}R^{27}$, may, independently, form a 4-7 membered heterocyclic ring selected from the group: azetidine (itself optionally

substituted by hydroxy or C_{1-4} alkyl), pyrrolidine, piperidine, azepine, 1,4-morpholine or 1,4-piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen; R^{12}, R^{25}, R^{28} and R^{31} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

provided that when X is CH_2 and m and n are both 0 then Y is not NR^{35};

or an N-oxide thereof; or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen includes fluorine, chlorine, bromine and iodine.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl, iso-propyl or tert-butyl. Alkyl groups preferably comprise 1-6 carbon atoms.

Alkenyl is, for example, vinyl or allyl. Alkenyl groups preferably comprise 2-6 carbon atoms.

Alkynyl is, for example, propargyl. Alkynyl groups preferably comprise 2-6 carbon atoms.

Cycloalkyl is monocyclic and is, for example, cyclopropyl, cyclopentyl or cyclohexyl. Cycloalkyl groups preferably comprise 3-6 carbon atoms.

Cycloalkyl fused to a benzene ring is, for example, bicyclo[4.2.0]octa-1,3,5-trienyl.

Aryl is preferably phenyl or naphthyl.

Heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulfur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl, 1,6-dihydropyridinyl (for example in a 6-oxo-1,6-dihydropyridinyl moiety), pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), 2,3-dihydrobenz[b]thienyl (for example in a 1,1-dioxo-2,3-dihydrobenz[b]thienyl moiety), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 1,2-dihydrobenzthiazolyl (for example in a 1H-benzthiazol-2-one-yl moiety), 2,3-dihydrobenzthiazolyl (for example in a 2,3-dihydrobenzthiazol-2-one-yl moiety), 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2-a]pyridinyl), thieno[3,2-b]pyridin-6-yl, 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, 3,4-dihydro-1H-2,1-benzothiazinyl (for example in a 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl moiety), a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine, 3,7-dihydro-purinyl (for example in a 3,7-dihydro-purin-2,6-dione-8-yl moiety), quinolinyl, isoquinolinyl, 1,2-dihydroisoquinolinyl (for example in a 2H-isoquinolin-1-one-yl (alternatively called 1-oxo-1,2-dihydroisoquinolinyl or 1,2-dihydroisoquinolinyl-1-one) moiety), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), 1,4-dihydro[1,8]naphthyridinyl (for example in a 1H-[1,8]naphthyridin-4-one-yl moiety), or a benzothiazinyl, 4H-benzo[1,4]thiazinyl (for example in a 4H-benzo[1,4]thiazin-3-one-yl moiety); or an N-oxide thereof (such as a pyridine N-oxide), or an S-oxide or S-dioxide thereof. 1,2-Dihydropyridinyl (an alternative numbering for a 1,6-dihydropyridinyl) can also be present in a 2-oxo-1,2-

dihydropyridinyl moiety; and 2,3-dihydro-1H-indazolyl can also be present in a 3-oxo-2,3-dihydro-1H-indazolyl moiety.

Heterocyclyl also includes cinnolinyl, phthalazinyl, 3,4-dihydrophthalazinyl (for example in a 4-oxo-3,4-dihydrophthalazinyl moiety), benzoxazinyl, 2,3-dihydro-4H-1,4-benzoxazinyl (for example in a 3-oxo-2,3-dihydro-4H-1,4-benzoxazinyl moiety), 3,4-dihydro-2H-1,4-benzoxazinyl (for example in a 3-oxo-3,4-dihydro-2H-1,4-benzoxazinyl moiety), isoindolyl, 1,3-dihydro-2H-isoindolyl (for example in a 1,3-dioxo-1,3-dihydro-2H-isoindolyl moiety), pyrazolotriazinyl (for example pyrazolo[5,1-c][1,2,4]triazinyl), pyrazinyl, pyridazinyl, 9H-purinyl, pyrazolopyrimidinyl (for example pyrazolo[1,5-a]pyrimidinyl), imidazobenzothiazolyl (for example imidazo[2,1-b][1,3]benzothiazolyl), 1,2,5-oxadiazolyl, imidazopyrimidinyl (for example imidazo[1,2-a]pyrimidinyl), quinolinyl, 1,2-dihydroquinolinyl (for example in a 2-oxo-1,2-dihydroquinolinyl moiety) or 2,1,3-benzoxadiazolyl (for example as a 1-oxide); or it may additionally be an N-oxide thereof, or an S-oxide or S-dioxide thereof. Further examples of heterocyclyl are 1,3-benzothiazole, 2,3-dihydro-1,3-benzothiazole (for example in a 2-oxo-2,3-dihydro-1,3-benzothiazole moiety), 4,5,6,7-tetrahydroindazole, 2,3-dihydro-1H-benzimidazole (for example in a 2-oxo-2,3-dihydro-1H-benzimidazole moiety) and 1,4-dihydroquinoline (for example in a 4-oxo-1,4-dihydroquinoline moiety).

An N-oxide of a compound of formula (I) or (Ia) is, for example, a 1-oxy-piperidinyl compound.

Heteroaryl is an aromatic heterocyclyl. Thus it is, for example furyl, thienyl, pyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyrimidinyl, indolyl, benzo[b]furyl, benz[b]thienyl, indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl, thieno[3,2-b]pyridin-6-yl 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan, quinoxalinyl, a pyrazolopyridine, a purine, quinolinyl, isoquinolinyl, a naphthyridinyl, a benzothiazinyl, cinnolinyl, phthalazinyl, benzoxazinyl, isoindolyl, pyrazolotriazinyl pyrazinyl, pyridazinyl, pyrazolopyrimidinyl, imidazobenzothiazolyl, imidazopyrimidinyl quinolinyl or 2,1,3-benzoxadiazolyl; or an N-oxide thereof (such as a pyridine N-oxide), or an S-oxide or S-dioxide thereof.

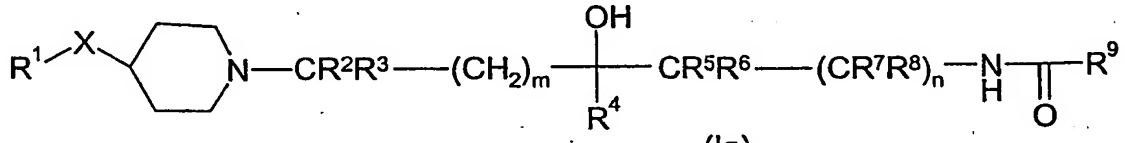
Haloalkyl is an alkyl group carrying one or more (such as 1 to 6) halogen atoms and is, for example, CF_3. Alkoxyalkyl is, for example, CH_3OCH_2, $CH_3CH_2OCH_2$ or $CH_3CH_2O(CH_2)_2$. Haloalkyloxy is an alkoxy group carrying one or more (such as 1 to 6)

halogen atoms and is, for example, OCF_3. Alkoxyalkoxy is, for example, CH_3OCH_2O, $CH_3CH_2OCH_2O$ or $CH_3CH_2O(CH_2)_2O$. Phenylalkyl is, for example, benzyl, phenyleth-1-yl or phenyleth-2-yl. Phenylalkoxy is, for example benzyloxy. Heteroarylalkyl is, for example, pyridinylmethyl or pyrimidinylmethyl. Heteroaryloxy is, for example, pyridinyloxy or pyrimidinyloxy. Heteroarylalkoxy is, for example, pyridinylmethoxy or pyrimidinylmethoxy.

In one aspect the present invention provides a compound of formula (I) wherein: X is CH_2, O, $S(O)_2$ or NR^{10}; Y is a bond, CH_2, NR^{35}, CH_2NH, $CH_2NHC(O)$, $CH(OH)$, $CH(NHC(O)R^{33})$, $CH(NHS(O)_2R^{34})$, CH_2O or CH_2S; Z is C(O), or when Y is a bond Z can also be $S(O)_2$; R^1 is optionally substituted aryl, optionally substituted heterocyclyl or C_{4-6} cycloalkyl fused to a benzene ring; R^4 is hydrogen, C_{1-6} alkyl (optionally substituted by C_{3-6} cycloalkyl) or C_{3-6} cycloalkyl; R^2, R^3, R^5, R^6, R^7 and R^8 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl; m and n are, independently, 0 or 1; R^9 is optionally substituted aryl or optionally substituted heterocyclyl; R^{10}, R^{32}, R^{33} and R^{35} are, independently, hydrogen or C_{1-6} alkyl; R^{34} is C_{1-6} alkyl; wherein the foregoing aryl and heterocyclyl moieties are, where possible, optionally substituted by: halogen, cyano, nitro, hydroxy, oxo, $S(O)_kR^{12}$, $OC(O)NR^{13}R^{14}$, $NR^{15}R^{16}$, $NR^{17}C(O)R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, $S(O)_2NR^{22}R^{23}$, $NR^{24}S(O)_2R^{25}$, $C(O)NR^{26}R^{27}$, $C(O)R^{28}$, CO_2R^{29}, $NR^{30}CO_2R^{31}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{1-6} alkylthio, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halogen, hydroxy, nitro, $S(O)_r$(C_{1-4} alkyl), $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; k and r are, independently, 0, 1 or 2; R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27}, R^{29}, R^{30}, and R^{31} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen,

hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3); alternatively $NR^{13}R^{14}$, $NR^{15}R^{16}$, $NR^{20}R^{21}$, $NR^{22}R^{23}$, $NR^{26}R^{27}$, may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, 1,4-morpholine or 1,4-piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen; R^{12}, R^{25} and R^{28} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3); provided that when X is CH_2 and m and n are both 0 then Y is not NR^{35}; or an N-oxide thereof; or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

In another aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein: X is CH_2, O, $S(O)_2$ or NR^{10}; R^1 is optionally substituted aryl or optionally substituted heterocyclyl; R^4 is hydrogen, C_{1-6} alkyl (optionally substituted by C_{3-6} cycloalkyl) or C_{3-6} cycloalkyl; R^2, R^3, R^5, R^6, R^7 and R^8 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl; m and n are, independently, 0 or 1; R^9 is optionally substituted

aryl or optionally substituted heterocyclyl; R^{10} is hydrogen or C_{1-6} alkyl; wherein the foregoing aryl and heterocyclyl moieties are, where possible, optionally substituted by: halogen, cyano, nitro, hydroxy, oxo, $S(O)_kR^{12}$, $OC(O)NR^{13}R^{14}$, $NR^{15}R^{16}$, $NR^{17}C(O)R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, $S(O)_2NR^{22}R^{23}$, $NR^{24}S(O)_2R^{25}$, $C(O)NR^{26}R^{27}$, $C(O)R^{28}$, CO_2R^{29}, $NR^{30}CO_2R^{31}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{1-6} alkylthio, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halogen, hydroxy, nitro, $S(O)_r$(C_{1-4} alkyl), $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; k and r are, independently, 0, 1 or 2; R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27}, R^{29}, R^{30}, and R^{31} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3); alternatively $NR^{13}R^{14}$, $NR^{15}R^{16}$, $NR^{20}R^{21}$, $NR^{22}R^{23}$, $NR^{26}R^{27}$, may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, 1,4-morpholine or 1,4-piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen; R^{12}, R^{25} and R^{28} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl),

$C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$; $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3); or an N-oxide thereof; or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

In a further aspect the present invention provides a compound of formula (I) wherein: X is O; Y is a bond, CH_2, NR^{35}, CH_2NH, CH(OH), $CH(NHC(O)R^{33})$, $CH(NHS(O)_2R^{34})$ or CH_2O; Z is C(O), or when Y is a bond Z can also be $S(O)_2$; R^1 is optionally substituted phenyl; R^4 is hydrogen or C_{1-6} alkyl; R^2, R^3, R^5, R^6, R^7 and R^8 are, when present, all hydrogen; m and n are, independently, 0 or 1; R^9 is optionally substituted aryl or optionally substituted heterocyclyl; R^{32} and R^{35} are, independently, hydrogen or C_{1-6} alkyl; R^{33} and R^{34} are C_{1-6} alkyl; wherein the foregoing phenyl, aryl and heterocyclyl moieties are, where possible, optionally substituted by: halogen, cyano, hydroxy, oxo, $S(O)_2R^{12}$, $NR^{15}R^{16}$, $NR^{17}C(O)R^{18}$, $S(O)_2NR^{22}R^{23}$, $NR^{24}S(O)_2R^{25}$, $C(O)NR^{26}R^{27}$, CO_2R^{29}, C_{1-6} alkyl (itself optionally mono-substituted by NHC(O)phenyl), CF_3, OCF_3, phenyl or heteroaryl;wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3; R^{15}, R^{16}, R^{17}, R^{18}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27} and R^{29} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy) or C_{3-6} cycloalkyl; alternatively $NR^{22}R^{23}$ may form an azetidine ring (itself optionally substituted by hydroxy or C_{1-4} alkyl); R^{12} and R^{25} are, independently, C_{1-6} alkyl or phenyl; or a pharmaceutically acceptable salt thereof.

In a still further aspect R^1 is phenyl optionally substituted (for example with one, two or three of) by halogen (especially fluoro or chloro), cyano, C_{1-4} alkyl (especially methyl), C_{1-4} alkoxy (especially methoxy), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2NH(C_{3-6}$ cycloalkyl), $C(O)_2(C_{1-4}$ alkyl), $C(O)NH(C_{1-4}$ alkyl) or $C(O)NH_2$.

In another aspect R^1 is phenyl optionally substituted (for example with one, two or three of) by halogen (especially fluoro or chloro), cyano, C_{1-4} alkyl (especially methyl) or C_{1-4} alkoxy (especially methoxy). In a further aspect R^1 is phenyl substituted by one, two or three of: fluoro, chloro, methyl or cyano. In another aspect R^1 is phenyl substituted by

one, two or three of: fluoro, chloro or methyl. Thus, R^1 is, for example, 2-methyl-4-chlorophenyl, 3-methyl-2,4-dichlorophenyl, 3,4-difluorophenyl, 3-fluoro-4-chlorophenyl or 4-chlorophenyl. In a still further aspect R^1 is 3,4-dichlorophenyl.

In another aspect X is O.

In yet another aspect Y is a bond.

In another aspect Z is C(O).

In a further aspect m is 0.

In a still further aspect n is 0.

In another aspect m and n are both 0.

In another aspect R^4 is hydrogen or C_{1-6} alkyl (such as methyl). In yet another aspect R^4 is hydrogen.

In yet another aspect R^2, R^3, R^5, R^6, R^7 and R^8 are all hydrogen; and in a further aspect n is 0, and R^2, R^3, R^5 and R^6 are all hydrogen.

In a further aspect R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are, when present, all hydrogen.

In a still further aspect R^9 is mono- or di- substituted phenyl, unsubstituted heterocyclyl or mono- or di- substituted heterocyclyl, the substituents being chosen from those described above.

In another aspect R^9 is optionally substituted heterocyclyl wherein the heterocyclyl group is: thienyl, pyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,5-oxadiazolyl, pyridinyl, 1,6-dihydropyridinyl (for example in a 6-oxo-1,6-dihydropyridinyl or a 2-oxo-1,2-dihydropyridinyl moiety), pyrimidinyl, indolyl, indazolyl, 2,3-dihydro-1H-indazolyl (for example in a 3-oxo-2,3-dihydro-1H-indazolyl moiety), an imidazopyridinyl (such as imidazo[1,2-a]pyridinyl), 2,1,3-benzothiadiazolyl, quinoxalinyl, quinolinyl, 1,2-dihydroquinolinyl (for example in a 2-oxo-1,2-dihydroquinolinyl moiety), 1,4-dihydroquinoline (for example in a 4-oxo-1,4-dihydroquinoline moiety), isoquinolinyl, 1,2-dihydroisoquinolinyl (for example in a 2H-isoquinolin-1-one-yl (alternatively called 1-oxo-1,2-dihydroisoquinolinyl or 1,2-dihydroisoquinolinyl-1-one) moiety), cinnolinyl, 3,4-dihydrophthalazinyl (for example in a 4-oxo-3,4-dihydrophthalazinyl moiety), 2,3-dihydro-4H-1,4-benzoxazinyl (for example in a 3-oxo-2,3-dihydro-4H-1,4-benzoxazinyl moiety), 3,4-dihydro-2H-1,4-benzoxazinyl (for example in a 3-oxo-3,4-dihydro-2H-1,4-benzoxazinyl moiety), 1,3-dihydro-2H-isoindolyl (for example in a 1,3-dioxo-1,3-dihydro-2H-isoindolyl moiety), pyrazolotriazinyl (for example pyrazolo[5,1-c][1,2,4]triazinyl), pyrazolopyrimidinyl (for example pyrazolo[1,5-a]pyrimidinyl), imidazobenzothiazolyl (for

example imidazo[2,1-b][1,3]benzothiazolyl), imidazopyrimidinyl (for example imidazo[1,2-a]pyrimidinyl), or 2,1,3-benzoxadiazolyl (for example as a 1-oxide), 1,3-benzothiazole, 2,3-dihydro-1,3-benzothiazole (for example in a 2-oxo-2,3-dihydro-1,3-benzothiazole moiety), 4,5,6,7-tetrahydroindazole or 2,3-dihydro-1H-benzimidazole (for example in a 2-oxo-2,3-dihydro-1H-benzimidazole moiety).

In yet another aspect the aryl (such as phenyl) or heterocyclyl group R^9 is unsubstituted or substituted by one or more of: oxo (where possible), halogen, C_{1-4} alkyl, CF_3, C_{1-4} alkoxy, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ or OCF_3.

In a further aspect when R^9 is heterocyclyl it is an optionally substituted thienyl, quinolinyl, 1,2-dihydroquinolinyl, 1,3-benzthiazolyl, 2,3-dihydro-1,3-benzothiazolyl, imidazo[1,2-a]pyridinyl, isoquinolinyl or 1,2-dihydroisoquinolinyl; or a 1,2-dihydropyridone, a 1,6-dihydropyridone, a pyrazolyl, a pyrrolyl or an indolyl.

In yet another aspect R^9 is phenyl or heterocyclyl (as defined anywhere above), either of which is optionally substituted by: halo, hydroxy, nitro, cyano, oxo, amino, C_{1-4} alkyl (itself optionally substituted by $S(O)_2(C_{1-4}$ alkyl) or $S(O)_2$phenyl), C_{1-4} alkoxy, $S(O)_kR^{12}$ {wherein k is 0, 1 or 2 (preferably 2); and R^{12} is C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) (such as cyclopropylmethyl) or phenyl}, $C(O)NH_2$, $NHS(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl) or $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above).

In another aspect R^{32} is hydrogen.

In a further aspect R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27}, R^{29}, R^{30}, and R^{31} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen or C_{1-4} alkyl) or heterocyclyl (itself optionally substituted by halogen or C_{1-4} alkyl); and R^{12}, R^{25} and R^{28} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen or C_{1-4} alkyl) or heterocyclyl (itself optionally substituted by halogen or C_{1-4} alkyl).

In a still further aspect R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27}, R^{29} and R^{30} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen or C_{1-4} alkyl) or heterocyclyl (itself optionally substituted by

halogen or C_{1-4} alkyl); and R^{12}, R^{25}, R^{28} and R^{31} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen or C_{1-4} alkyl) or heterocyclyl (itself optionally substituted by halogen or C_{1-4} alkyl).

In yet another aspect R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27}, R^{29} and R^{30} are, independently, hydrogen or C_{1-6} alkyl; and R^{12}, R^{25}, R^{28} and R^{31} are, independently, C_{1-6} alkyl (optionally substituted by hydroxy)or phenyl.

In a further aspect R^{10} is hydrogen.

In another aspect R^{35} is hydrogen or C_{1-6} alkyl (such as methyl); (for example R^{35} is hydrogen).

In yet another aspect R^{33} is C_{1-6} alkyl (such as methyl).

In a further aspect R^{34} is C_{1-6} alkyl (such as methyl).

In a still further aspect the present invention provides a compound of formula (I) or (Ia) wherein: R^1 is phenyl optionally substituted by 2 halogens (such as chlorine); X is O; m is 0; n is 0 or 1; R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are all hydrogen; and R^9 is phenyl, thienyl, quinolinyl, 1,3-benzthiazolyl, 2,3-dihydro-1,3-benzothiazolyl, imidazo[1,2-a]pyridinyl or 1,2-dihydroisoquinolinyl optionally substituted by $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$), halogen (for example chlorine or fluorine), NH_2, C_{1-4} alkoxy (such as OCH_3), cyano or, where possible, oxo.

In another aspect the present invention provides a compound of formula (I) or (Ia) wherein: R^1 is phenyl optionally substituted by 1 or 2 halogens (such as chlorine), or by 1 or 2 halogens (such as chlorine) and a C_{1-4} alkyl (such as methyl); X is O; m is 0; n is 0 or 1; R^2, R^3, R^4, R^5 and R^6, and, when present, R^7 and R^8 are all hydrogen; and R^9 is phenyl, thienyl, quinolinyl, 1,3-benzthiazolyl, 2,3-dihydro-1,3-benzothiazolyl, imidazo[1,2-a]pyridinyl, 1,2-dihydroisoquinolinyl, 1,2-dihydropyridinyl, 1,6-dihydropyridinyl or pyrazolyl, all optionally substituted by $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and the two alkyl groups may join together to form an azetidine ring), halogen (for example chlorine or fluorine), NH_2, C_{1-4} alkyl (such as CH_3), C_{1-4} alkoxy (such as OCH_3), CF_3, cyano or, where possible, oxo.

In a further aspect the present invention provides a compound of formula (I) or (Ia) wherein: R^1 is phenyl optionally substituted by 1 or 2 halogens (such as chlorine), and optionally substituted by 0 or 1 C_{1-6} alkyl (such as methyl); X is O; m is 0; n is 0 or 1; R^2, R^3, R^4, R^5 and R^6, and, when present, R^7 and R^8 are all hydrogen; and R^9 is phenyl, thienyl,

quinolinyl, 1,3-benzthiazolyl, 2,3-dihydro-1,3-benzothiazolyl, imidazo[1,2-a]pyridinyl, 1,2-dihydroisoquinolinyl, 1,2-dihydropyridinyl, 1,6-dihydropyridinyl, pyrazolyl, pyrrolyl or indolyl, all of which are optionally substituted by $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, halogen (for example chlorine or fluorine), NH_2, C_{1-4} alkoxy (such as OCH_3), C_{1-4} alkyl (such as methyl), CF_3, OCF_3, cyano or, where possible, oxo.

In a still further aspect the present invention provides a compound of formula (I) or (Ia) wherein: R^1 is phenyl optionally substituted by 1 or 2 halogens (such as chlorine), and optionally substituted by 0 or 1 C_{1-6} alkyl (such as methyl); X is O; m is 0; n is 0 or 1; R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are all hydrogen; and R^9 is phenyl, thienyl, quinolinyl, 1,3-benzthiazolyl, 2,3-dihydro-1,3-benzothiazolyl, imidazo[1,2-a]pyridinyl or 1,2-dihydroisoquinolinyl, all of which are optionally substituted by $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$), halogen (for example chlorine or fluorine), NH_2, C_{1-4} alkoxy (such as OCH_3), C_{1-4} alkyl (such as methyl), CF_3, OCF_3, cyano or, where possible, oxo.

In another aspect the present invention provides a compound of formula (I) or (Ia) wherein R^9 is isoquinolinyl, 1-oxo-1,2-dihydroisoquinolinyl, quinolinyl, 2-oxo-1,2-dihydroquinolinyl, 2-oxo-1,2-dihydropyridinyl, 6-oxo-1,6-dihydropyridinyl or pyrazolyl; each optionally substituted by halogen (such as fluorine), C_{1-4} alkyl (such as methyl or ethyl), CF_3, C_{1-4} alkoxy (such as methoxy), $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ or OCF_3.

In a further aspect the present invention provides a compound of formula (I) or (Ia) wherein R^9 is isoquinolinyl, 1-oxo-1,2-dihydroisoquinolinyl, quinolinyl or 2-oxo-1,2-dihydroquinolinyl; each optionally substituted by halogen (such as fluorine), C_{1-4} alkyl (such as methyl or ethyl), CF_3, C_{1-4} alkoxy (such as methoxy), $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$) or OCF_3.

In a still further aspect R^9 is 1-oxo-1,2-dihydroisoquinolinyl optionally substituted by halogen (such as fluorine), C_{1-4} alkyl (such as methyl or ethyl), CF_3, C_{1-4} alkoxy (such as methoxy), $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$) or OCF_3. Alternatively, R^9 is 2-oxo-1,2-dihydroquinolinyl optionally substituted by halogen (such as fluorine), C_{1-4} alkyl (such as methyl or ethyl), CF_3, C_{1-4} alkoxy (such as methoxy), $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$) or OCF_3.

In another aspect R^9 is an oxo-substituted dihydropyridinyl (such as 6-oxo-1,6-dihydropyridin-3-yl, 2-oxo-1,2-dihydropyridin-5-yl or 2-oxo-1,2-dihydropyridin-4-yl), an

oxo-substituted dihydroisoquinolinyl (such as 1-oxo-1,2-dihydroisoquinolin-4-yl), an oxo-substituted dihydrophthalazinyl (such as 4-oxo-3,4- dihydrophthalazin-1-yl), pyrazinyl (such as pyrazin-4-yl), pyrrolyl (such as pyrrol-3-yl) or indolyl (such as indol-3-yl), each of which is not further substituted or substituted by: halogen (such as chloro or fluoro), C_{1-4} alkyl (such as methyl), CF_3 or C_{3-5} cycloalkyl (such as cyclopropyl).

In a further aspect R^9 is an oxo-substituted dihydropyridinyl (such as 6-oxo-1,6-dihydropyridin-3-yl, 2-oxo-1,2-dihydropyridin-5-yl or 2-oxo-1,2-dihydropyridin-4-yl), an oxo-substituted dihydroisoquinolinyl (such as 1-oxo-1,2-dihydroisoquinolinyl-4-yl) or pyrazinyl (such as pyrazin-4-yl), each of which is not further substituted or substituted by: halogen (such as chloro or fluoro), C_{1-4} alkyl (such as methyl) or CF_3.

An example of a compound of formula (I) or (Ia) is:

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylsulfonyl)benzamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(methylsulfonyl)benzamide;

2-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(methylsulfonyl)benzamide;

4-amino-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-methoxybenzamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(methylsulfonyl)benzamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(methylsulfonyl)thiophene-2-carboxamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoline-6-carboxamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-2,3-dihydro-1,3-benzothiazole-6-carboxamide acetate salt;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-fluoroimidazo[1,2-*a*]pyridine-2-carboxamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,3-benzothiazole-6-carboxamide;

3-cyano-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

N-{4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-3-hydroxybutyl}-2-(methylsulfonyl)benzamide;

N-{4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-3-hydroxybutyl}-2-oxo-2,3-dihydro-1,3-benzothiazole-6-carboxamide;

4-amino-*N*-{4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-3-hydroxybutyl}-3-methoxybenzamide;

N-{4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxybutyl}-2-(methylsulfonyl)benzamide;

N-{(2R)-3-[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylsulfonyl)benzamide;

N-{(2R)-3-[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*S*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylsulfonyl)benzamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-[(methylamino)sulfonyl]benzamide;

3,5-bis(acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

3-(Acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-pyrazole-4-carboxamide;

2-(Acetylamino)-5-bromo-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-1,2-dihydropyridine-3-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-5-carboxamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-indole-4-carboxamide;

2-(Acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

2-(Acetylamino)-5-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

2-(Acetylamino)-4-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

5-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulphonyl)amino]benzamide;

4-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulphonyl)amino]benzamide;

2-Amino-4-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

5-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-6-oxo-1,6-dihydropyridine-3-carboxamide;

2-(Aminosulphonyl)-4-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*1H*-indazole-3-carboxamide;

1-*tert*-Butyl-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-methyl-*1H*-pyrazole-5-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4,5,6,7-tetrahydro-*2H*-indazole-3-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(*1H*-pyrazol-3-yl)benzamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}cinnoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-hydroxyquinoline-4-carboxamide;

N-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-oxo-3,4-dihydrophthalazine-1-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-indole-3-carboxamide;

N-{(2*R*)-3-[4-(4-Chlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylsulfonyl)benzamide;

N-{(2*R*)-3-[4-(4-Chlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(4-Chloro-3-fluorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Difluorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*N*-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*N*-methyl-1*H*-indazole-3-carboxamide;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*N*-methyl-4-oxo-3,4-dihydrophthalazine-1-carboxamide;

Benzoic acid, 3-[[2-[[(2*R*)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]amino]-2-oxoethyl]amino]-, methyl ester ;

Propanamide, *N*-[2-[[2-[[(2*R*)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]amino]-2-oxoethyl]amino]phenyl]-;

Propanamide, *N*-[2-[[2-[[(2*R*)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]amino]-2-oxoethyl]amino]phenyl]-;

(2*S*)-*N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-hyroxy-2-phenylethanamide;

2-[2-({(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)-2-oxoethoxy]benzamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(3-oxo-2,3-dihydro-*4H*-1,4-benzoxazin-4-yl]acetamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methoxybenzamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylamino)benzamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}nicotinamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}isonicotinamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(dimethylamino)benzamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-hydroxynicotinamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(1H-indol-3-yl)acetamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4,7-dimethylpyrazolo[5,1-c][1,2,4]triazine-3-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}pyrazine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-9H-purine-6-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoline-6-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,7-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(pyrimidin-2-ylthio)acetamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-fluoro-1H-indole-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,3-benzothiazole-6-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-phenyl-1,3-oxazole-4-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-hydroxypyridine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-hydroxypyridine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-benzimidazole-5-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-indole-5-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-methyl-1H-indole-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-imidazole-4-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-indole-6-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-methyl-1H-indole-3-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-indole-7-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-[(methylamino)sulfonyl]benzamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3,4-bis(methylsulfonyl)benzamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-pyridin-3-ylacetamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-hydroxy-1H-indole-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,5-dimethyl-1H-pyrazole-3-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(methylsulfonyl)-1H-indole-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoxaline-6-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,8-naphthyridine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}imidazo[2,1-b][1,3]benzothiazole-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,6-dimethylimidazo[1,2-a]pyridine-3-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-oxo-2,3-dihydro-1H-indazole-4-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-hydroxy-1H-indazole-6-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(1H-benzimidazol-1-yl)-N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}acetamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-ethyl-3-methyl-1H-pyrazole-5-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-methyl-1H-pyrazole-3-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-methyl-1,2,5-oxadiazole-3-carboxamide;

6-chloro-N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}imidazo[1,2-a]pyridine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}imidazo[1,2-a]pyrimidine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(4-methylpyrimidin-2-yl)thio]acetamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-hydroxyquinoline-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoline-8-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-methylimidazo[1,2-a]pyridine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}imidazo[1,2-a]pyridine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,6-naphthyridine-2-carboxamide;

N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,1,3-benzoxadiazole-5-carboxamide 1-oxide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-1,6-dihydropyridine-3-carboxamide;

4-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-pyrazole-3-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-phenyl-1,3-oxazole-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3,5-dimethyl-1*H*-pyrazole-4-carboxamide;

(2*R*)-2-(Acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-phenylethanamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(2-hydroxyphenyl)acetamide;

(2*R*)-*N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulfonyl)amino]-2-phenylethanamide;

(2*S*)-2-(Acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-phenylethanamide;

(2*S*)-*N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulfonyl)amino]-2-phenylethanamide;

1-{(R)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-o-tolyl-urea;

1-{(R)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-p-tolyl-urea;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-2-oxo-1,2-dihydroquinoline-4-carboxamide;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-4-oxo-3,4-dihydrophthalazine-1-carboxamide;

(2*S*)-*N*-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-2-hydroxy-2-phenethanamide;

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-((2*R*)-3-{4-[2-(Aminocarbonyl)-3,4-dichlorophenoxy]piperidin-1-yl}-2-hydroxypropyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

3-Cyano-*N*-{(2*S*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide;

5-[({(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)-sulfonyl]-2-methoxybenzamide;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-sulfonamide acetate salt;

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,4-difluorobenzenesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}methanesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-phenylmethanesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-methoxybenzenesulfonamide;

N-({5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-2-thienyl}methyl)benzamide;

4-cyano-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide;

N-{5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-4-methyl-1,3-thiazol-2-yl}acetamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}thiophene-2-sulfonamide;

4-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]benzoic acid;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,5-dimethoxybenzenesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(phenylsulfonyl)thiophene-2-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(1,3-oxazol-5-yl)thiophene-2-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]thiophene-2-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-pyridin-2-ylthiophene-2-sulfonamide;

5-chloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,3-dimethyl-1H-pyrazole-4-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3,5-dimethylisoxazole-4-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,1,3-benzothiadiazole-4-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-methyl-1H-imidazole-4-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,1,3-benzoxadiazole-4-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-isoxazol-3-ylthiophene-2-sulfonamide;

methyl 3-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]thiophene-2-carboxylate;

2,6-dichloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-methylbenzenesulfonamide;

3-chloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}propane-2-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}propane-1-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-methyl-1-phenyl-1H-pyrazole-4-sulfonamide;

3-chloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methylbenzenesulfonamide;

methyl 5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-2-methyl-3-furoate;

methyl 5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-1-methyl-1H-pyrrole-2-carboxylate;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3,4-dimethoxybenzenesulfonamide;

5-chloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}thiophene-2-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-morpholin-4-ylpyridine-3-sulfonamide;

N-{2-chloro-4-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]phenyl}acetamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydroxyquinoxaline-6-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,4-dimethoxybenzenesulfonamide;

5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-2-methoxybenzamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methylbenzenesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,4-dimethyl-1,3-thiazole-5-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-hydroxyquinoxaline-6-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}pyridine-3-sulfonamide;

4'-cyano-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}biphenyl-2-sulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,2-dimethyl-1H-imidazole-4-sulfonamide;

4-acetyl-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(methylsulfonyl)benzenesulfonamide;

2-chloro-4-cyano-N-{(2S)-3-[4-(3,4-dichlorophenoxy)-piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide;

N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,3,5-trimethyl-1H-pyrazole-4-sulfonamide;

N-[(2*R*)-3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxamide;

N-{(2*S*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate;

N-{(2*S*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*S*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-[(methylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-{[(2-hydroxyethyl)amino]sulfonyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

7-[(Cyclopropylamino)sulfonyl]-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

7-(Azetidin-1-ylsulfonyl)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

7-(Aminosulfonyl)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-[(dimethylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-[(3-hydroxy-3-methylazetidin-1-yl)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate;

N-[(2*R*)-3-(4-{3,4-Dichloro-2-[(cyclopropylamino)carbonyl]phenoxy}piperidin-1-yl)-2-hydroxypropyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

N-{(2*R*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-((2*R*)-2-Hydroxy-3-{4-[4-(methylsulfonyl)phenoxy]piperidin-1-yl}propyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(4-Cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-((2*R*)-3-{4-[2-(Aminocarbonyl)-4-chlorophenoxy]piperidin-1-yl}-2-hydroxypropyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-[(2*R*)-3-(4-{4-Chloro-2-[(methylamino)carbonyl]phenoxy}piperidin-1-yl)-2-hydroxypropyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

Methyl 5-chloro-2-{[1-((2*R*)-2-hydroxy-3-{[(1-oxo-1,2-dihydroisoquinolin-4-yl)carbonyl]amino}propyl)piperidin-4-yl]oxy}benzoate acetate salt;

N-((2*R*)-3-{4-[2-(Aminosulfonyl)-3,4-dichlorophenoxy]piperidin-1-yl}-2-hydroxypropyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide trifluoroacetate salt;

N-[(2*R*)-3-(4-{3,4-Dichloro-2-[(methylamino)sulfonyl]phenoxy}piperidin-1-yl)-2-hydroxypropyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

N-[(2*R*)-3-(4-{3,4-Dichloro-2-[(cyclopropylamino)sulfonyl]phenoxy}piperidin-1-yl)-2-hydroxypropyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

N-{(2*R*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-{4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-6-(methylsulphonyl)-1*H*-indole-3-carboxamide;

N-{(2*R*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(methylsulphonyl)-1*H*-indole-3-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide;

N-((2*R*)-3-{4-[3,4-Dichloro-2-(methylsulfonyl)phenoxy]piperidin-1-yl}-2-hydroxypropyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt;

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide acetate salt;

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide acetate salt;

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(2-oxoquinoxalin-1(2*H*)-yl)acetamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-oxo-3,4-dihydroquinoxaline-1(2*H*)-carboxamide;

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide;

N-{(2*R*)-3-[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide;

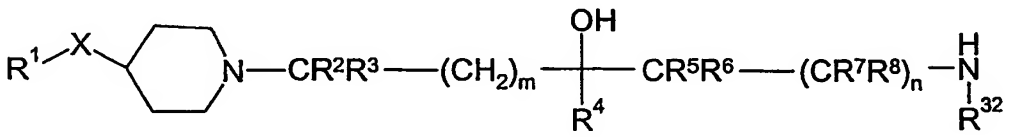
N-{(2*R*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl}-2-hydroxypropyl}-1-oxo-1,2-dihydro-2-methylisoquinoline-4-carboxamide;

N-{(2*R*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-1,2-dihydro-1-methylquinoline-4-carboxamide;

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-8-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide; or,

N-{(2*R*)-3-[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-8-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide.

A compound of formula (I) or (Ia) can be prepared by reacting a compound of formula (II):



(II)

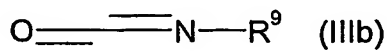
wherein X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{32}, m and n are as defined above, with:

(i) when Y is a bond, CH_2, NR^{35}, CH_2NH, $CH_2NHC(O)$, CH(OH), $CH(NHCOR^{33})$, $CH(NHSO_2R^{34})$, CH_2O or CH_2S, Z is C(O), R^{35} is not hydrogen and, R^{33} and R^{34} are as defined above, a compound of formula (IIIa):

$$L^1—CO—Y—R^9 \quad \text{(IIIa)}$$

wherein R^9 is as defined above and L^1 is a leaving group (for example a hydroxyl or chloride leaving group) in the presence of a base (for example di*iso*propylelthylamine), optionally in the presence of a coupling agent (for example bromo-tris-pyrrolidinophosphonium hexafluorophosphate, PyBrOP or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate); and,

(ii) when Y is NH and Z is C(O), a compound of formula (IIIb):



(IIIb)

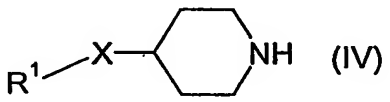
wherein R^9 is as defined above.

(iii) when Y is a bond and Z is $S(O)_2$, a compound of formula (IIIc):

$$L^1 — S(O)_2 — R^9 \qquad (IIIc)$$

wherein R^9 is as defined above and L^1 is a leaving group (for example a hydroxyl or chloride leaving group) in the presence of a base (for example pyridine).

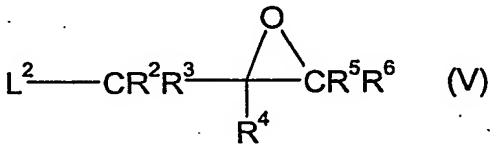
A compound of formula (II) can be prepared as described in WO 00/58305 or WO 01/77101, or by reacting a compound of formula (IV):



(IV)

wherein X and R^1 are as defined above, with:

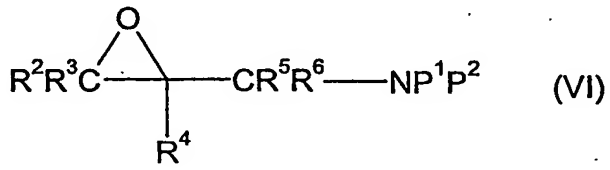
(i) when m and n are 0, R^2, R^3, R^5 and R^6 are hydrogen, and R^4 and R^{32} are as defined for formula (I), a compound of formula (V):



(V)

in which L^2 is a leaving group (for example chloro or nosyloxy{3-NO_2-C_6H_4-$S(O)_2O$-}) followed by reaction with ammonia, an amine R^{32}-NH_2 or with sodium azide and subsequent reduction with, for example, triphenylphosphine;

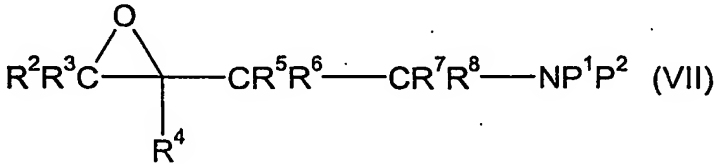
(ii) when m and n are 0, R^2 and R^3 are hydrogen and R^4, R^5, R^6 and R^{32} are as defined for formula (I), with a compound of formula (VI):



(VI)

in which P^1 and P^2 are, alone or together, suitable protective groups (for example together they form phthalamide), or either P^1 or P^2 is R^{32}, followed by deprotection using, for example when P^1 and P^2 form phtalamide, hydrazine;

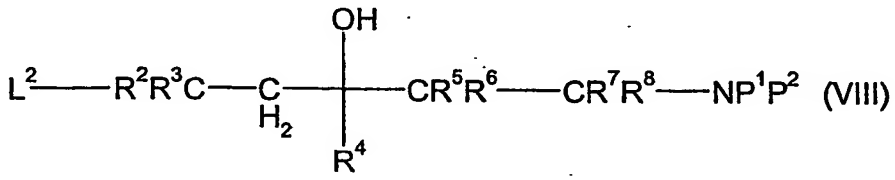
(iii) when m is 0, n is 1, R^2 and R^3 are hydrogen and R^4, R^5, R^6, R^7, R^8 and R^{32} are as defined for formula (I), with a compound of formula (VII):



(VII)

in which P^1 and P^2 are, alone or together, suitable protective groups (for example together they form phthalamide), or either P^1 or P^2 is R^{32}, followed by deprotection using, for example when P^1 and P^2 form phtalamide, hydrazine;

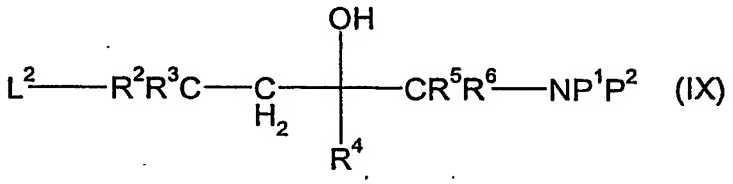
(iv) when m and n are 1, R^2 and R^3 are hydrogen and R^4, R^5, R^6, R^7, R^8 and R^{32} are as defined for formula (I), with a compound of formula (VIII):



(VIII)

in which L^2 is as defined for formula (V) and P^1 and P^2 are, alone or together, suitable protective groups (for example together they form phthalamide), or either P^1 or P^2 is R^{32}, followed by deprotection using, for example when P^1 and P^2 form phthalamide, hydrazine;

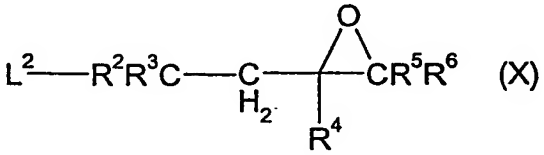
(v) when m is 1 and n is 0, R^2 and R^3 are hydrogen, R^5 and R^6 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, and R^4 and R^{32} are as defined for formula (I), with a compound of formula (IX):



(IX)

in which L^2 is as defined for formula (V) and P^1 and P^2 are, alone or together, suitable protective groups (for example together they form phthalamide), or either P^1 or P^2 is R^{32}, followed by deprotection using, for example when P^1 and P^2 form phthalamide, hydrazine;

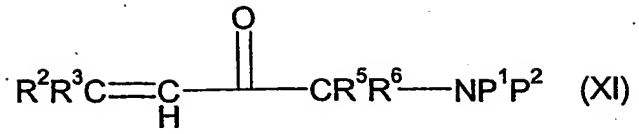
(vi) when m is 1 and n is 0, R^2, R^3, R^5 and R^6 are hydrogen and R^4 and R^{32} are as defined for formula (I), with a compound of formula (X):



(X)

in which L^2 is a leaving group (for example bromine) followed by reaction with ammonia, an amine R^{32}-NH_2 or with sodium azide and subsequent reduction with, for example, triphenylphosphine;

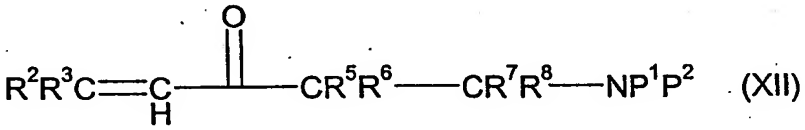
(vii) when m is 1 and n is 0, R^2, R^3, R^5 and R^6 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, and R^1, R^4 and R^{32} are as defined for formula (I), with a compound of formula (XI):



(XI)

in which P^1 and P^2 are, alone or together, suitable protective groups (for example together they form phthalamide), or either P^1 or P^2 is R^{32}, followed by hydride reduction (for example with sodium borohydride), or by adding an appropriate organometallic species (for example R^4MgX, where X is a halide); or,

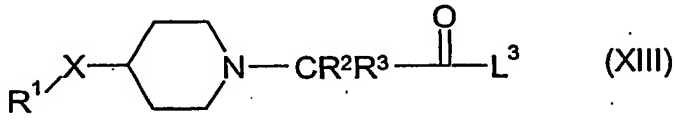
(viii) when m is 1 and n is 1, R^2, R^3, R^5 R^6, R^7 and R^8 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, and R^1, R^4 and R^{32} are as defined for formula (I), with a compound of formula (XII):



(XII)

in which P^1 and P^2 are, alone or together, suitable protective groups (for example together they form phthalamide), or either P^1 or P^2 is R^{32}, followed by hydride reduction (for example with sodium borohydride), or by adding an appropriate organometallic species (for example R^4MgW, where W is a halide).

When m is 0 and n is 0, R^2, R^3, R^5 and R^6 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, compounds or formula (II) can be prepared by reacting a compound of formula (XIII):



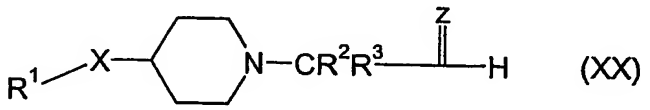
(XIII)

wherein X and R^1 are as defined for formula (I), and L^3 is hydrogen or a leaving group (for example ethoxy, N,O-dimethylhydroxylamine), with a compound of formula (XIV):

(XIV)

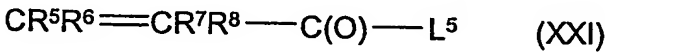
in which M represents a metal (for example Li or Na) and L^4 is an amino group (for example ammonium) followed by rearrangement (for example with phenyliodonium diacetate, Tetrahedron Letters, 2001, 42, 1449.) and appropriate reduction (for example with sodium borohydride), or an appropriate organometalic addition (for example R^4MgW, where W is a halide).

When m is 0, n is 1 and R^2, R^3, R^5, R^6, R^7 and R^8 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, compounds of formula (II) can be prepared by reacting a compound of formula (XX):



(XX)

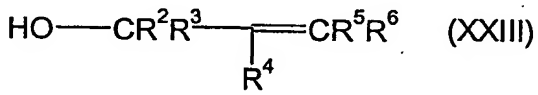
wherein X, R^1 and R^4 are as described in formula (I) above and Z is an aldehyde protective group (for example cyanohydrin or dithiane), with a compound of formula (XXI):



(XXI)

in which R^5, R^6, R^7 and R^8 are as described above, and L^5 is an alkoxy or amino group (for example ethoxy or ammonium) in presence of a base (for example LDA or *n*-butylithium), followed by hydrolytic removal of the group L^5, rearrangement (for example with phenyliodonium diacetate) and appropriate reduction (for example with sodium borohydride), or an appropriate organometalic addition (for example R^4MgW, where W is a halide).

A compound of formula (V) can be prepared by reacting a compound of formula (XXII):

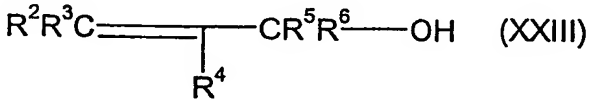


(XXIII)

with a peracid (for example *meta*-chloroperbenzoic acid) or using Sharpless asymmetric epoxidation conditions (J. Am. Chem. Soc. 1980, 102, 5974-5976), followed by activation of the alcohol as a leaving group (for example as nosyloxy).

A compound of formula (VI) can be prepared:

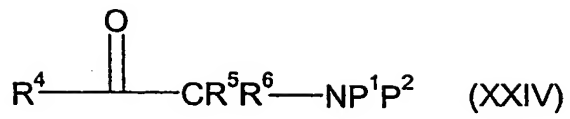
(a) when both R^5 and R^6 are hydrogen, by reacting a compound of formula (XXIII):



(XXIII)

with a peracid (for example *meta*-chloroperbenzoic acid) or using Sharpless asymmetric epoxidation conditions, followed, for example, by a Mitsunobu reaction using phthalimide, 1,1-(azodicarbonyl)dipiperidine and tributylphosphine (Tetrahedron Lett. 1993, 34, 1639).

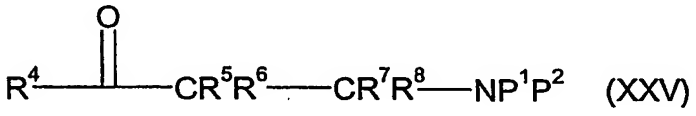
(b) when R^5 and R^6 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, by reacting a compound of formula (XXIV):



(XXIV)

in which P^1 and P^2 are, alone or together, suitable protective groups (for example together they form phthalamide), or either P^1 or P^2 is R^{32}, with a sulphur ylide (for example trimethylsulfoniummethylide, J. Am. Chem. Soc. 1965, 87, 1353-1364); or a phosphonium ylide (for example tiphenylphosphoniummethylide); followed by epoxidation of the resulting alkene using a peracid (for example *meta*-chloroperbenzoic acid).

A compound of formula (VII) can be prepared by reacting a compound of formula (XXV):



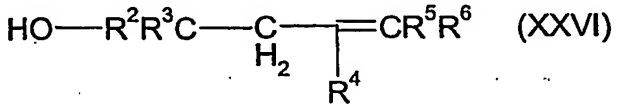
(XXV)

in which P^1 and P^2 are, alone or together, suitable protective groups (for example together they form phthalamide), or either P^1 or P^2 is R^{32}, with a sulfur ylide (for example trimethylsulfoniummethylide), or a phosphonium ylide (for example tiphenylphosphoniummethylide) followed by epoxidation of the resulting alkene using a peracid (for example *meta*-chloroperbenzoic acid).

A compound of formula (VIII) can be prepared by reacting a compound of formula (XXV) with the anion of ethyl acetate (which can be prepared by the action of lithium diisopropylamide on ethyl acetate) followed by reduction of the resulting ester, or with, for example, vinyl magnesium Grignard and subsequent hydroboration (for example cathechol borane)/oxidation (for example hydrogen peroxide) of the alkene.

A compound of formula (IX) can be prepared from a compound of formula (XXIV) in a similar way as for compound (VIII).

A compound of formula (X) can be prepared by reacting a compound of formula (XXVI):



(XXVI)

with a peracid (for example *meta*-chloroperbenzoic acid), followed by selective activation of the primary alcohol as a leaving group (for example nosyloxy).

Further, compounds of formula (I) and (Ia) can be prepared by or by routine adaptation of: the routes described above, methods described in the art, or the Examples

recited below. The intermediates identified above are commercially available or can be prepared by using or adapting methods described in the art.

In a further aspect of the invention there is provided a process for preparing 4-(3,4-dichlorophenoxy)piperidine comprising the steps of:

a. reacting 4-hydroxypiperidine with a suitable base in a suitable solvent at room temperature; and,

b. heating the mixture so produced together with 1,2-dichloro-4-fluorobenzene at a temperature in the range 50-90°C, or at reflux of the solvent used.

In a further aspect the present invention provides a process for preparing 4-(3,4-dichlorophenoxy)piperidine comprising reacting 4-hydroxypiperidine with a suitable base {such as an alkali metal (preferably sodium or potassium) C_{1-10} alkoxide [such as a C_{4-10} tertiary alkoxide (for example a C_{4-6} tertiary alkoxide)], for example potassium *tert*-butoxide or potassium 3,7-dimethyl-3-octanoxide} in a suitable solvent {such as: an ether [for example tetrahydrofuran or methyl *tert*-butyl ester], an aromatic solvent [such as toluene] or a mixture of these solvents} at room temperature (10-30°C); heating the mixture so produced together with 1,2-dichloro-4-fluorobenzene at a temperature in the range 50-90°C, or at reflux of the solvent used.

In a still further aspect the present invention provides a process for preparing 4-(3,4-dichlorophenoxy)piperidine comprising reacting 4-hydroxypiperidine with a suitable base {such as an alkali metal (preferably sodium or potassium) C_{1-10} alkoxide (such as a C_{4-10} tertiary alkoxide), for example a C_{1-6} alkoxide (such as a C_{4-6} tertiary alkoxide), for example potassium *tert*-butoxide} in a suitable solvent {such as: an ether [for example tetrahydrofuran or methyl *tert*-butyl ester], an aromatic solvent [such as toluene] or a mixture of these solvents} at room temperature (10-30°C), and heating the mixture so produced to a temperature in the range 50-90°C, or at reflux of the solvent used, and adding 1,2-dichloro-4-fluorobenzene.

Examples of tertiary alkoxides are potassium *tert*-butoxide and potassium 3,7-dimethyl-3-octanoxide.

In another aspect the present invention provides processes for the preparation of compounds of formula (I) and (Ia).

The intermediates of formula (VI), (VII) and (VIII) defined herein are novel and these intermediates, and processes for their preparation, are provided as further features of the invention.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

In one aspect examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

The compounds of the invention are also H1 antagonists and may be used in the treatment of allergic disorders.

The compounds of the invention may also be used to control a sign and/or symptom of what is commonly referred to as a cold (for example a sign and/or symptom of a common cold or influenza or other associated respiratory virus infection).

According to a further feature of the invention there is provided a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR3 receptor activity), or antagonising H1, in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula (I) or (Ia), or a pharmaceutically acceptable salt thereof or a solvate thereof.

The invention also provides a compound of the formula (I) or (Ia), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament.

In another aspect the invention provides the use of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR3 receptor activity), or antagonising H1, in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma

(for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

In a further aspect a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example

late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

The present invention also provides the use of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma or rhinitis.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR3 mediated disease state, especially asthma) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR3 receptor) activity or antagonising H1, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or (Ia), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For

these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of $0.01 mgkg^{-1}$ to $100 mgkg^{-1}$ of the compound, preferably in the range of $0.1 mgkg^{-1}$ to $20 mgkg^{-1}$ of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) when given, ^1H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO-D6 (CD_3SOCD_3), methanol-D4 (CD_3OD) or $CDCl_3$ as the solvent unless otherwise stated;

(ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB) or electrospray (ESI); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the title and sub-title compounds of the examples and methods were named using the ACD/Index name program version 4.55 from Advanced Chemistry Development, Inc;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry,

NovaPak or Xterra reverse phase silica column; and

(v) the following abbreviations are used:

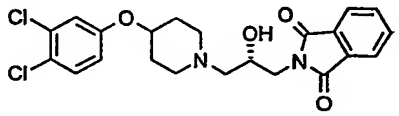
APCI	Atmospheric pressure CI
DMF	N,N-dimethylformamide
HPLC	High pressure liquid chromatography
MTBE	Methyl *tert*-butyl ether

DMSO	dimethylsulfoxide
THF	tetrahydrofuran
DCM	dichloromethane

Preparation 1

(2R)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol

Step 1: 2-{(2*S*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-isoindole-1,3(2*H*)-dione

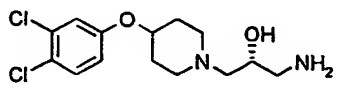


(R)-2-(Oxiranylmethyl)-1*H*-isoindole-1,3(2*H*)-dione (*Tetrahedron Asymmetry,* **1996**, *7*, 1641, 5g) in a mixture of 50 ml of ethanol and 15 ml of DMF was treated with 4-(3,4-dichlorophenoxy)-piperidine (6g). The mixture was stirred overnight at room temperature. The solution was concentrated under vacuum and the residue was azeotroped twice with toluene. The crude material was purified by chromatography (ethyl acetate) to give the subtitle compound as a yellow oil.

MS (APCI) 449/451 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.92-7.81(2H, m), 7.77-7.70 (2H, m), 7.30 (1H, d), 6.98 (1H, t), 6.74 (1H, dt), 4.34-4.20 (1H, m), 4.09-3.97 (1H, m), 3.83 (1H, dd), 3.73 (1H, dd), 2.93-2.79 (1H, m), 2.73-2.60 (1H, m), 2.59-2.37 (3H, m), 2.31 (1H, t), 2.02-1.86 (2H , m), 1.86-1.67 (2H, m).

Step 2: (2*R*)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol



(S)-2-[3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]-1*H*-isoindole-1,3(2*H*)-dione (4g) in ethanol (100ml) was treated with 20 ml of hydrazine monohydrate and the resulting mixture was refluxed for 3h. The reaction was cooled and filtered. The

filtrate was evaporated and the product was chromatographed (ethyl acetate) to give the title compound as a yellow oil which solidified on standing (2.5g).

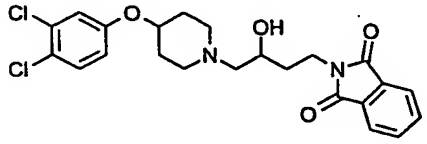
MS (APCI) 319/321 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 7.00 (1H, d), 6.75 (1H, dd), 4.00 (1H, app. sept.), 3.74-3.62 (1H, m), 2.94-2.84 (1H, m), 2.82 (1H, d), 2.72-2.61 (1H, m), 2.65 (1H, d); 2.60-2.49 (1H, m), 2.46-2.21(3H, m), 2.06-1.91 (2H, m), 1.90-1.72 (2H, m).

Preparation 2

4-Amino-1-[4-(3,4-dichlorophenoxy)piperidin-1-yl]butan-2-ol

Step 1: 2-{4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-3-hydroxybutyl}-1*H*-isoindole-1,3(2*H*)-dione

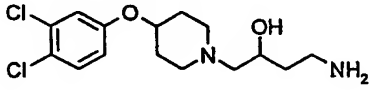


A mixture of 4-(3,4-dichlorophenoxy)piperidine *(WO 0058305, WO 0177101)* (4.40g) and 2-(2-oxiran-2-ylethyl)-1*H*-isoindole-1,3(2*H*)-dione *(J. Med. Chem.* **1979**, *22(6),* 631-9. 5.00g) in ethanol (50 ml) was stirred at 60°C for 12h. The mixture was cooled down and left overnight. The formed crystals were collected by filtration, washed with cold ethanol and dried under *vacuum* to afford the sub-title compound as a white solid (3.0g).

MS (APCI) 463/465 $(M+H)^+$

^{1}H NMR δ (DMSO) 7.90-7.80 (4H, m), 7.49 (1H, d), 7.25 (1H, d), 6.97 (1H, dd), 4.53-4.33 (2H, m), 3.80-3.69 (1H, m), 3.69-3.58 (2H, m), 2.77-2.60 (2H, m), 2.38-2.17 (4H, m), 1.94-1.84 (2H, m), 1.85-1.75 (1H, m), 1.65-1.50 (3H, m).

Step 2: 4-amino-1-[4-(3,4-dichlorophenoxy)piperidin-1-yl]butan-2-ol



A solution of mixture of 2-{4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-3-hydroxybutyl}-1*H*-isoindole-1,3(2*H*)-dione (3.00g) in a mixture of ethanol (75 ml) and 35% aqueous hydrazine (15 ml) was heated at reflux 4h. The mixture was cooled down and the solvents removed under *vacuum*. The residue was triturated with warm

dichloromethane. The white solid was removed by filtration and the filtrate dried over sodium sulfate. The mixture was filtered and the solvent was evaporated to afford the title compound as a yellow oil (2.10g) which was used without further purification in the next step.

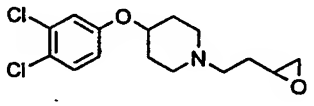
MS (APCI) 333/335 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.29 (1H, d), 6.96 (1H, d), 6.76 (1H, dd), 4.40-4.25 (1H, m), 3.95-3.85 (1H, m), 3.20-3.00 (2H, m), 2.96-2.79 (1H, m), 2.78-2.63 (1H, m), 2.60-2.45 (1H, m), 2.41-2.23 (3H, m), 2.10-1.88 (2H, m), 1.88-1.70 (3H, m), 1.70-1.58 (1H, m).

Preparation 3

1-Amino-4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]butan-2-ol

Step 1: 4-(3,4-dichlorophenoxy)-1-(2-oxiran-2-ylethyl)piperidine

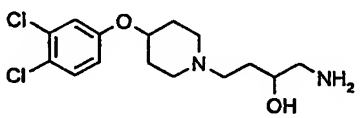


A mixture of 4-(3,4-dichlorophenoxy)piperidine *(WO 0058305, WO 0177101)* (2.00g), 2-(2-bromoethyl)oxirane *(J. Am. Chem. Soc. 1981, 103, 7520-8)* (1.36g) and potassium carbonate (2.2 g) in acetone (20 ml) was stirred at 50°C for 12h. The solvent was removed under vacuum. The residue was partitioned between water and ethyl acetate. The organic layer was washed with water, brine and dried over magnesium sulfate. The mixture was filtered and the solvent was evaporated to afford the sub-title compound as a yellow oil (2.50g) which was used without further purification in the next step.

MS (APCI) 316/318 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 7.00 (1H, d), 6.75 (1H, dd), 4.27 (1H, dquintet), 3.02-2.95 (1H, m), 2.78 (1H, t), 2.77-2.68 (2H, m), 2.57-2.49 (3H, m), 2.39-2.24 (2H, m), 2.03-1.94 (2H, m), 1.87-1.75 (2H, m), 1.77-1.72 (1H, m), 1.73-1.61 (1H, m).

Step 2: 1-amino-4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]butan-2-ol



In a sealed metal tube, a solution of 4-(3,4-dichlorophenoxy)-1-(2-oxiran-2-ylethyl)piperidine (1.00g) in 7N ammonia in methanol (25 ml) was heated at 70°C for 12h. The solvent was removed under vacuum and the residue purified on silicagel (0 to 10% 7N

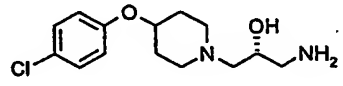
ammonia in methanol/dichloromethane) to afford the title compound as a yellow oil (0.55g).

MS (APCI) 333/335 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 4.36-4.27 (1H, m), 3.79-3.70 (1H, m), 2.93-2.78 (1H, m), 2.76-2.59 (5H, m), 2.61-2.50 (1H, m), 2.37-2.27 (1H, m), 2.03-1.90 (2H, m), 1.89-1.76 (2H, m), 1.74-1.61 (1H, m), 1.54-1.46 (1H, m).

Preparation 4

(2*R*)-1-Amino-3-[4-(4-chlorophenoxy)piperidin-1-yl]propan-2-ol

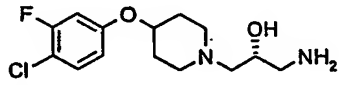


Prepared as described in Preparation 1.

^{1}H NMR δ (CD_3OD) 7.13 (2H, d), 6.80 (2H, d), 4.26 (1H, septet), 3.68-3.59 (1H, m), 2.77-2.65 (2H, m), 2.62 (1H, dd), 2.46 (1H, dd), 2.38-2.24 (4H, m), 1.95-1.85 (2H, m), 1.73-1.61 (2H, m).

Preparation 5

(2*R*)-1-Amino-3-[4-(4-chloro-3-fluorophenoxy)piperidin-1-yl]propan-2-ol



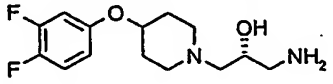
Prepared as described in Preparation 1.

MS (ESI) 303/305 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.32 (1H, t), 6.86 (1H, dd), 6.77 (1H, ddd), 4.40 (1H, quintet), 3.74 (1H, ddd), 2.87-2.75 (2H, m), 2.72 (1H, dd), 2.56 (1H, dd), 2.50-2.37 (4H, m), 2.08-1.95 (2H, m), 1.85-1.72 (2H, m).

Preparation 6

(2*R*)-1-Amino-3-[4-(3,4-difluorophenoxy)piperidin-1-yl]propan-2-ol



Prepared as described in Preparation 1.

MS (ESI) 287 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.14 (1H, dt), 6.87 (1H, ddd), 6.75-6.69 (1H, m), 4.35 (1H, septet), 3.80-3.71 (1H, m), 2.88-2.75 (2H, m), 2.75 (1H, dd), 2.58 (1H, dd), 2.51-2.34 (4H, m), 2.07-1.94 (2H, m), 1.85-1.71 (2H, m).

Preparation 7

2R)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol.

Step 1: 4-(3,4-dichlorophenoxy)piperidine

4-Hydroxypiperidine (50g, 494mmol) was added portionwise to a stirred suspension of potassium *tert*-butoxide (110.9g, 990mmol) in THF (900ml) at room temperature and under nitrogen. The mixture was heated at reflux and 1,2-dichloro-4-fluorobenzene (98g, 594mmol) added dropwise over 30 minutes. The mixture was stirred at reflux for another 1 hour then cooled down to room temperature, diluted with ethyl acetate (500ml) and washed with water (500ml). The organic phase was diluted further with ethyl acetate (500ml) and extracted with 1M hydrochloric acid (200ml). The aqueous extract was adjusted to pH>10 by addition of a solution of sodium hydroxide and extracted twice with *tert*-butylmethyl ether (750ml). The organic extracts were dried over magnesium sulfate, filtered and concentrated under vacuum to yield the sub-title compound as a dark oil which was used as such in the next step.

MS (ESI) 246/248 $(M+H)^+$

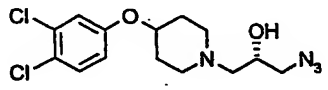
^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 7.00 (1H, d), 6.78 (1H, dd), 4.29-4.37 (1H, m), 3.15 (2H, dt), 2.75 (2H, td), 1.97-2.03 (2H, m), 1.60-1.70 (2H, m).

Alternative Step 1: 4-(3,4-dichlorophenoxy)piperidine

A thin slurry of 4-hydroxypiperidine (50g, 494mmol) in THF (200ml) was added to a stirred suspension of potassium *tert*-butoxide (110.9g, 990mmol) in THF (650ml) at room temperature and washed in with THF (50ml). The resultant mixture was stirred under nitrogen for 20 minutes. 1,2-Dichloro-4-fluorobenzene (98g, 594mmol) was added and the resultant mixture heated at reflux for 90 minutes. The reaction mixture was cooled to room temperature and water (500ml) added. The layers were separated and the solvent removed from the organic fraction. The material was then partitioned between MTBE and 10% aqueous citric acid solution. The layers separated and the aqueous layer washed with further MTBE (2x250ml). The aqueous phase was basified to pH>10 by addition of 10N NaOH solution and the product extracted with iso-propyl acetate (2x300ml). The organics

were washed with brine (300ml), dried over magnesium sulfate, filtered and concentrated under vacuum to yield the sub-title compound as a dark oil which was used as such in the next step (109.1g, 90%).

Step 2: (2S)-1-azido-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol



(2*R*)-Oxiran-2-ylmethyl 3-nitrobenzenesulfonate (21.1g, 81.3mmol) in DMF (300ml) was treated with triethylamine (22.6ml, 163.0mmol) followed by 4-(3,4-dichlorophenoxy)-piperidine (20g, 81.3mmol). The mixture was stirred overnight at 60°C. Sodium azide (16g, 243.9mmol) was added to the mixture and the reaction was stirred for a further 72h. The solution was carefully concentrated under vacuum and the residue was diluted with water (600ml), extracted with ethyl acetate (1500ml). The organic layer was washed twice with water (500ml), then brine (200ml) and concentrated under vacuum to afford an oil.

Step 3: (2*R*)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol

The resulting oil from Step 2 was dissolved in wet tetrahydrofuran (225ml) and was treated with triphenylphosphine (53.3g, 203mmol). The reaction was heated at 60°C and stirred for 4h. The solvent was removed under vacuum, the residue re-dissolved into 2N hydrochloric acid (1000ml) and the aqueous layer was extracted with ethyl acetate (3 times 700ml). The aqueous phase was basified with a 2N sodium hydroxide solution and extracted with dichloromethane (3 times 1000ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by chromatography (8% 7N ammonia in methanol/DCM) to give the title compound as a yellow oil (17g).

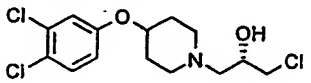
MS (APCI) 319/321 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 7.00 (1H, d), 6.75 (1H, dd), 4.0 (1H, app. sept.), 3.74-3.62 (1H, m), 2.94-2.84 (1H, m), 2.82 (1H, d), 2.72-2.61 (1H, m), 2.65 (1H, d), 2.60-2.49 (1H, m), 2.46-2.21 (3H, m), 2.06-1.91 (2H, m), 1.90-1.72 (2H, m).

Preparation 8

(2R)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol

Step1: (2*S*)-1-Chloro-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol

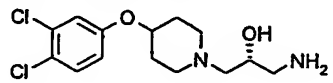


(S)-(+)-Epichlorohydrin (3.50ml, 44.7mmol) was added to a stirred solution of 4-(3,4-dichlorophenoxy)piperidine (10.0g, 40.6mmol) in ethanol (50ml). After 20h, water (50ml) was added. The mixture stirred for a further 2h then the precipitated solid was collected by filtration, washed with water and dried under vacuum at 50°C for 2h to give the sub-title compound.

MS (ESI) 338/340/342/344 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 7.00 (1H, d), 6.75 (1H, dd), 4.28-4.33 (1H, m), 3.89-3.96 (1H, m), 3.54-3.62 (3H, m), 2.84-2.92 (1H, m), 2.65-2.72 (1H, m), 2.45-2.59 (3H, m), 2.32-2.36 (1H, m), 1.90-2.01 (2H, m), 1.77-1.87 (2H, m).

Step 2: (2*R*)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol



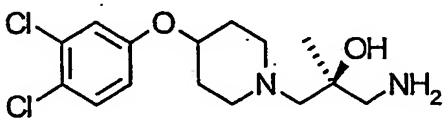
A solution of sodium hydroxide (1.62g, 40.6mmol) in methanol (200ml) was added to the product of the previous step and the mixture stirred for 1h whereupon all solid had dissolved. Aqueous ammonia solution (28%, 80ml) was added and stirring continued at ambient temperature for 3 days. The solution was concentrated *in vacuo* to a volume of 100ml then dissolved in hydrochloric acid (0.5M, 800ml) and extracted with diethyl ether (2 × 200ml). The aqueous extract was filtered to remove insoluble impurities then made alkaline by addition of sodium hydroxide and extracted with dichloromethane (4 × 200ml) with filtration of the two-phase mixture to remove further insoluble impurities. Organic extracts were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to provide the title compound as an oil (10.6g).

MS (APCI) 319/321 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 7.00 (1H, d), 6.75 (1H, dd), 4.0 (1H, app. sept.), 3.74-3.62 (1H, m), 2.94-2.84 (1H, m), 2.82 (1H, d), 2.72-2.61 (1H, m), 2.65 (1H, d), 2.60-2.49 (1H, m), 2.46-2.21 (3H, m), 2.06-1.91 (2H, m), 1.90-1.72 (2H, m).

Preparation 9

(2*S*)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-methylpropan-2-ol



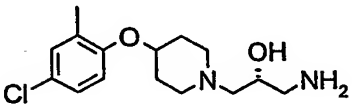
Prepared as described in Preparation 7 (Steps 2 and 3) using [(2R)-2-methyloxiran-2-yl]methyl-3-nitrobenzenesulfonate.

MS (APCI) 333/335 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.30 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 4.38-4.30 (1H, m), 3.48 (2H, s), 2.96-2.78 (2H, m), 2.62-2.30 (4H, m), 2.00-1.90 (2H, m), 1.85-1.72 (2H, m), 1.25 (3H, s).

Preparation 10

(2*R*)-1-Amino-3-[4-(4-chloro-2-methylphenoxy)-piperidin-1-yl]propan-2-ol



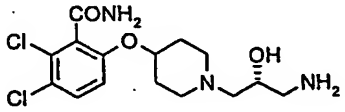
Prepared as described in Preparation 7 (Steps 2 and 3) from 4-(4-chloro-2-methylphenoxy)-piperidine.

MS (ESI) 299/301 $(M+H)^+$

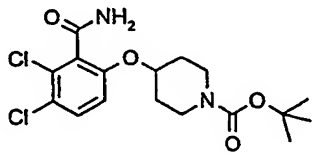
^{1}H NMR δ (CD_3OD) 7.12-7.05 (2H, m), 6.87 (1H, d), 4.39 (1H, septet), 3.77-3.70 (1H, m), 2.84-2.72 (2H, m), 2.71 (1H, dd), 2.55 (1H, dd), 2.50-2.39 (2H, m), 2.40 (1H, d), 2.39 (1H, d), 2.18 (3H, s), 2.04-1.95 (2H, m), 1.86-1.75 (2H, m).

Preparation 11

6-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)-2,3-dichlorobenzamide



Step 1: *tert*-Butyl 4-[2-(aminocarbonyl)-3,4-dichlorophenoxy]piperidine-1-carboxylate

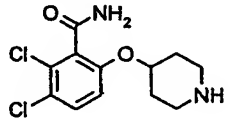


To a stirred solution of *tert*-butyl 4-[3,4-dichlorophenoxy]piperidine-1-carboxylate (7.0g, 20.3mmol) in dry THF (250ml) at -70°C under a nitrogen atmosphere was added dropwise *sec*-butyl lithium (18ml, 1.3M in cyclohexane). The solution was stirred a further 30min. at this temperature then treated with solid carbon dioxide pellets (excess). The cooling bath was removed and the mixture stirred vigorously whilst warming to room temperature over 1h. After a further 1h the solution was concentrated to ca 50ml volume then partitioned between aqueous sodium hydrogen carbonate solution and diethyl ether. The aqueous phase was further washed with diethyl ether (3 x), then acidified to pH 4 and extracted with dichloromethane (3 x). The combined extracts were dried (magnesium sulphate) and concentrated. Treatment of the crude carboxylic acid (2.5g, 6.4mmol) with carbonyl-1,1-diimidazolide (1.25g, 7.7mmol) in dichloromethane (50ml) at room temperature for 72h gave the crude imidazolide which was concentrated *in vacuo*, redissolved in ethanol (20ml) and treated with 35% aqueous ammonia (20ml) in an autoclave at 100°C for 2h. The mixture was allowed to cool to room temperature slowly to allow crystallization of the title compound. The crystalline product was filtered and washed with water. Recrystallization from ethanol/water gave the sub-title compound (1.90g).

MS (APCI) 289/291 $(M+H-BOC)^+$

^1H NMR δ ($CDCl_3$) 7.40 (1H, d), 6.83 (1H, d), 5.91 (1H, s), 5.73 (1H, s), 4.52 (1H, m), 3.59 (2H, m), 3.41 (2H, m), 1.86 (4H, m), 1.43 (9H, s).

Step 2: 2,3-dichloro-6-(piperidin-4-yloxy)benzamide



To a stirred solution of *tert*-butyl 4-[-[2-(aminocarbonyl)-3,4-dichlorophenoxy]piperidine-1-carboxylate (1.8g, 4.6mmol) in dichloromethane (10ml) was added trifluoroacetic acid (10ml). After 30min at room temperature the solution was concentrated *in vacuo* and partitioned between saturated aqueous sodium hydrogen carbonate solution and dichloromethane. The aqueous was re-extracted a further three times with dichloromethane and three times with ethy acetate. The combined organic extracts were dried (anhydrous potassium carbonate) and concentrated to afford the sub-title compound as a white solid (1.15g).

MS (APCI) 289/291 $(M+H)^+$

^1H NMR δ (CD_3OD) 7.49 (1H, d), 7.09 (1H, d), 4.65 (1H, M), 3.15 (2H, m), 2.84 (2H, m), 2.02 (2H, m), 1.82 (2H, m).

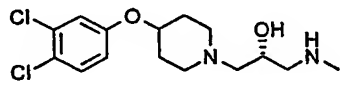
Step 3: 6-({1-[(2*R*)-3-amino-2-hydroxypropyl]piperidin-4-yl}oxy)-2,3-dichlorobenzamide

Step a: To a stirred solution of 2,3-dichloro-6-(piperidin-4-yloxy)benzamide (1.1g, 3.8mmol) in dimethylformamide (10ml) was added triethylamine (1.06ml. 7.6mmol) and (2R)-glycidyl-3-nitrobenzenesulfonate (1.0g, 3.8mmol) and the mixture heated at 60°C for 3h. Sodium azide (1.0g, 15.2mmol) was added and the temperature maintained for a further 48h. The mixture was concentrated *in vacuo* (blast shield) to almost dryness, and the product partitioned between dichloromethane and aqueous sodium hydrogen carbonate solution. The aqueous layer was reextracted with dichloromethane then with ethyl acetate. The combined organic extracts were dried (anhydrous potassium carbonate) and concentrated *in vacuo*.

Step b: The product was redissolved in tetrahydrofuran (50ml) and treated with water (5ml) and triphenylphosphine (2.4g). The mixture was heated at 60°C for 4h, then concentrated *in vacuo*. The product was partitioned between ethyl acetate and 1N aqueous hydrochloric acid. The aqueous extracts were washed further with ethyl acetate then basified with 48% sodium hydroxide solution to pH 11. The aqueous layer was extracted with dichloromethane (3 x), and the combined organic extracts dried (anhydrous potassium carbonate) and concentrated *in vacuo* to afford crude amine product which was used without any purification in the next step (See Example 132).

Preparation 12

(R)-1-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-3-methylamino-propan-2-ol



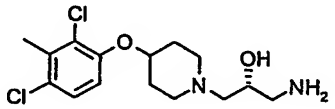
A solution of 4-(3,4-dichlorophenoxy)-1-[(2*R*)-oxiran-2-ylmethyl]piperidine (1g, 3.31mmol) and methylamine (2.56ml 40% in H_2O, 33.1mmol) in ethanol (15ml) was heated at 60°C in a sealed vessel for 16h. The solvent was evaporated at reduced pressure and the residue purified by flash column chromatography eluting with 8% 7M ammonia methanol in dichloromethane to give the title compound (875mg).

MS (APCI) 333/335 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 4.32-4.26 (1H, m), 3.86-3.80 (1H, m), 2.91-2.86 (1H, m), 2.71-2.65 (2H, m), 2.65 (1H, dd), 2.56-2.51 (2H, m), 2.54 (1H, dd), 2.48-2.42 (2H, m), 2.46 (3H, s), 2.38-2.27 (3H, m).

Preparation 13

(2*R*)-1-Amino-3-[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]propan-2-ol



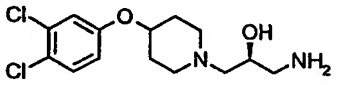
Prepared as described in Preparation 10 using 4-(2,4-dichloro-3-methylphenoxy)-piperidine.

MS (APCI) 333/335 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.25 (2H, d), 6.94 (2H, d), 4.54-4.37 (1H, m), 3.88-3.71 (1H, m), 3.35-3.24 (2H, m), 2.93-2.72 (4H, m), 2.72-2.57 (1H, m), 2.08-1.90 (2H, m), 1.92-1.75 (2H, m).

Preparation 14

(2*S*)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol



Prepared as described in Preparation 7 using (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate.

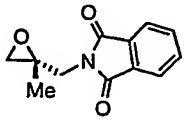
MS (ESI) 319/321 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.30 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 4.36-4.24 (1H, m), 3.75-3.65 (1H, m), 2.94-2.78 (2H, m), 2.70-2.60 (2H, m), 2.59-2.51 (1H, m), 2.41-2.25 (3H, m), 2.03-1.93 (2H, m), 1.87-1.77 (2H, m).

Preparation 15

(2*R*)-1-Amino-2-methyl-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol.

Step 1: 2-[[(2*R*)-2-methyloxiranyl]methyl]-1*H*-isoindole-1,3(2*H*)-dione.



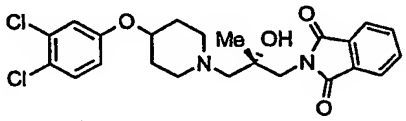
To a solution of (*2S*)-(2-methyloxiran-2-yl)methyl 3-nitrobenzenesulphonate (1.913g, 7mmoles) in dry dimethylformamide (15ml), was added potassium phthalimide (1.304g, 7mmoles). The mixture was stirred at 50°C for 5h and then cooled to room temperature. The resulting mixture was partitioned between ethyl acetate and water. The aqueous phase was washed with ethyl acetate (2x100ml) and the combined organic extracts were washed with water (3x100ml), saturated brine solution, dried over sodium sulfate and concentrated *in vacuo* to leave a crude orange wax. Purification by chromatography (silica, 20% ethyl acetate in *iso*-hexane) afforded the subtitle compound as a white solid (0.864g).

MS (ESI) 189 $(M\text{-}CO)^+$

^{1}H NMR δ ($CDCl_3$) 7.90-7.85 (2H, m), 7.78-7.71 (2H, m), 4.02 (1H, d), 3.71 (1H, d), 2.82 (1H, d), 2.62 (1H, d), 1.39 (3H, s).

Step 2:

2-[(*2R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl]-1*H*-isoindole-1,3(2*H*)-dione.



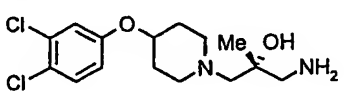
A solution of 4-(3,4-dichlorophenoxy)piperidine (0.985g, 4mmoles), 2-[[(*2R*)-2-methyloxiranyl]methyl]-1*H-iso*indole-1,3(2*H*)-dione (0.869g, 4mmoles) and triethylamine (0.809g, 1.12ml, 8mmoles) in ethanol (20ml) was stirred at 50°C for 5h. The resulting solution was cooled to room temperature and concentrated *in vacuo* to leave a crude yellow gum. Flash chromatography (silica, 2% of 7*N* methanolic ammonia in dichloromethane as eluant) afforded the subtitle compound as a yellow oil (1.24g).

MS (APCI) 463/465/467 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.89-7.85 (2H, m), 7.76-7.72 (2H, m), 7.30 (1H, d), 6.98 (1H, d), 6.78 (1H, dd), 4.27-4.21 (1H, m), 3.88 (1H,d), 3.70 (1H, d), 3.43 (1H, bd s), 2.96-2.81 (2H, m), 2.60-2.42 (4H, m), 1.95-1.89 (2H, m), 1.80-1.70 (2H, m), 1.15 (3H, s).

Step 3:

(*2R*)-1-Amino-2-methyl-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol.



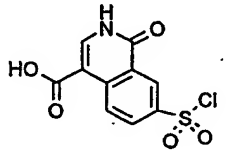
To a solution of 2-[(*2S*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl]-1*H*-*iso*indole-1,3(2*H*)-dione (278mg, 0.6mmoles) in ethanol (5ml) was added aqueous methylamine (40% wt. solution in water, 6ml). The mixture was stirred at room temperature for 24h and then concentrated *in vacuo* to leave a crude yellow glass. This glass was dissolved in methanol (2ml), added to an Isolute Flash SCX cartridge (2g), washed with methanol (25ml) and 7N ammonia in methanol (25ml). The methanolic ammonia was concentrated *in vacuo* to give the title compound as a yellow glass (165mg).

MS (ESI) 333/335/337 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 4.29-4.21 (1H, m), 2.96-2.80 (2H, m), 2.60-2.30 (4H, m), 2.00-1.90 (3H, m), 1.85-1.75 (3H, m), 1.13 (3H, s).

Preparation 16

7-(Chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



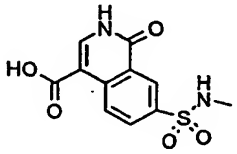
1-Oxo-7-sulfo-1,2-dihydroisoquinoline-4-carboxylic acid (5g) was added to chlorosulphonic acid (25ml). The mixture was heated at 100°C for 84h and then slowly dripped onto ice with stirring. The mixture was filtered and the residue was washed with water and ether and dried to yield 7-(chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid as a buff solid (7.5g).

MS (APCI) 286 $(M-H)^-$

^{1}H NMR δ (DMSO) 11.81 (1H, d), 8.79 (1H, d), 8.48 (1H, d), 8.03 (1H, d), 7.96 (1H, dd).

Preparation 17

7-[(Methylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



7-(Chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (1g) was added to aqueous methylamine (60ml) and the mixture was stirred for 18h. Concentrated

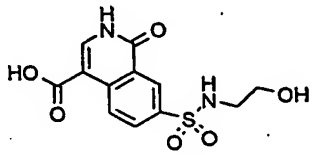
hydrochloric acid was added to acidify the mixture, which was filtered to yield 7-[(methylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid as a buff solid (0.84g).

MS (APCI) 283 $(M+H)^+$

^{1}H NMR δ (DMSO) 12.93 (1H, s), 12.13 (1H, d), 9.03 (1H, d), 8.61 (1H, d), 8.16 (1H, d), 8.12 (1H, dd), 7.65 (1H, q), 2.43 (3H, d).

Preparation 18

1,2-Dihydro-7-[[(2-hydroxyethyl)amino]sulfonyl]-1-oxo-4-isoquinolinecarboxylic acid



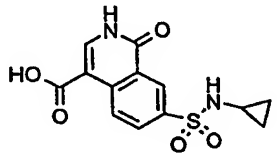
7-(Chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (1g) was added to ethanolamine(3ml) in tetrahydrofuran (3ml) and the mixture was stirred for 18h. Hydrochloric acid was added to acidify the mixture, which was filtered to yield 1,2-dihydro-7-[[(2-hydroxyethyl)amino]sulfonyl]-1-oxo-4-isoquinolinecarboxylic acid as a white solid.

MS (APCI) 313 $(M+H)^+$

^{1}H NMR δ (DMSO) 12.92 (5H, s), 12.12 (5H, s), 9.01 (6H, d), 8.62 (6H, s), 8.16 (13H, d), 8.13 (13H, dd), 7.81 (6H, t), 4.67 (5H, s), 3.39-3.25 (84H, m), 2.81 (13H, q).

Preparation 19

7-[(Cyclopropylamino)sulfonyl]-1,2-dihydro-1-oxo-4-isoquinolinecarboxylic acid



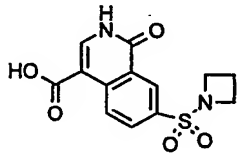
7-(Chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (1g) was added to cyclopropylamine(3ml) in tetrahydrofuran (20ml) and the mixture was stirred for 18h. Hydrochloric acid was added to acidify the mixture which was filtered to yield 7-[(cyclopropylamino)sulfonyl]-1,2-dihydro-1-oxo-4-isoquinolinecarboxylic acid as a white solid.

MS (APCI) 307 $(M-H)^-$

^{1}H NMR δ (DMSO) 12.93 (1H, s), 12.13 (1H, d), 9.03 (1H, d), 8.65 (1H, d), 8.16 (1H, d), 8.14 (1H, dd), 8.08 (1H, d), 2.13 (1H, dsextet), 0.48 (2H, td), 0.39-0.34 (2H, m).

Preparation 20

7-(Azetidin-1-ylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



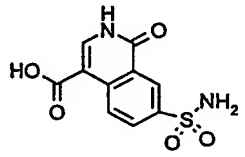
7-(Chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (1g) was added to azetidine (0.7ml) and diisopropylethylamine (0.4ml) in tetrahydrofuran (5ml) and acetonitrile (5ml) and the mixture was stirred for 72h then evaporated. The solid was crystallised from methanol then hydrochloric acid was added to acidify the mixture, which was filtered to yield 7-(azetidin-1-ylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid as a white solid.

MS (APCI) 309 $(M+H)^+$

^{1}H NMR δ (DMSO) 12.99 (1H, s), 12.21 (1H, d), 9.12 (1H, d), 8.54 (1H, d), 8.20 (1H, d), 8.16 (1H, dd), 3.70 (4H, t), 1.99 (2H, quintet).

Preparation 21

7-(Aminosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



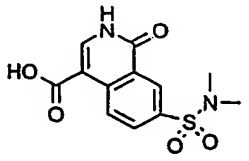
7-(Chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (1g) was added to 0.880 ammonia (60ml) and the mixture was stirred for 18h. Concentrated hydrochloric acid was added to acidify the mixture, which was filtered to yield 7-(aminosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid as a white solid.

MS (APCI) 269 $(M+H)^+$

^{1}H NMR δ (DMSO) 12.91 (1H, s), 12.08 (1H, d), 8.99 (1H, d), 8.68 (1H, d), 8.16 (1H, dd), 8.14 (1H, d), 7.53 (2H, s).

Preparation 22

7-[(Dimethylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



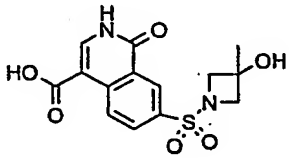
7-(Chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (0.8g) was added to dimethylamine (15ml) and the mixture was stirred for 18h. The mixture was acidified with concentrated hydrochloric acid and then filtered to yield 7-[(dimethylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid as a white solid.

MS (APCI) 295 $(M-H)^-$

^{1}H NMR δ (DMSO) 12.96 (1H, s), 12.19 (1H, d), 9.07 (1H, d), 8.50 (1H, d), 8.18 (1H, d), 8.11 (1H, dd), 2.65 (6H, s).

Preparation 23

7-[(3-Hydroxy-3-methylazetidin-1-yl)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



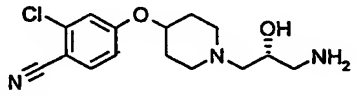
7-(Chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (1g), diisopropylethylamine (3ml) and 3-methylazetidin-3-ol hydrochloride (0.8g) in tetrahydrofuran (8ml) were heated at 55°C for 3 days. The mixture was acidified with hydrochloric acid and then filtered to yield 7-[(3-hydroxy-3-methylazetidin-1-yl)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid as a pale pink solid.

MS (ESI) 337 $(M-H)^-$

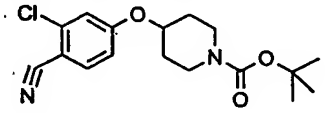
^{1}H NMR δ (DMSO) 12.99 (1H, s), 12.22 (1H, d), 9.11 (1H, d), 8.53 (1H, s), 8.21 (1H, d), 8.16 (1H, dd), 3.61 (2H, d), 3.46 (2H, d), 1.25 (3H, t).

Preparation 24

4-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)-2-chlorobenzonitrile



Step 1: *tert*-Butyl 4-(3-chloro-4-cyanophenoxy)piperidine-1-carboxylate



Potassium *tert*-butoxide (5.57g, 49.68mmol) was added to a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (5.00g, 24.84mmol) in glyme (100ml) and the mixture stirred for 30min. before addition of 2-chloro-4-fluoro-benzonitrile (7.73g, 49.68mmol). The reaction was stirred at room temperature overnight and then partitioned between ethyl acetate (250ml) and water (200ml). The organic layer was separated, dried over magnesium sulfate and the solvent evaporated. The residue was purified by flash chromatography eluting with ethyl acetate:isohexane (4:1) to give the subtitle compound as a colourless solid (3.45g).

MS (ESI) 337 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 1.47 (9H, s), 1.72-1.80 (2H, m), 1.90-1.97 (2H, m), 3.37 (2H, ddd), 3.68 (2H, ddd), 4.54 (1H, dquintet), 6.86 (1H, dd), 7.01 (1H, d), 7.57 (1H, d).

Step 2: 4-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)-2-chlorobenzonitrile

To a solution of the *tert*-butyl 4-(3-chloro-4-cyanophenoxy)piperidine-1-carboxylate (2.75g, 9.09mmol) in dichloromethane (20ml) was added trifluoroacetic acid (20ml) and the mixture stirred for 90 min.. The solvents were evaporated and the residue azeotroped with toluene (2x20ml) before dissolving in water (30ml) and addition of sodium hydroxide to bring the solution to pH 11. The free base was extracted with DCM (5x100ml). The organics were combined, dried over sodium sulfate and the solvent removed under reduced pressure to give a thick oil which was dissolved in DMF (30ml) before addition of (2R)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (2.35g, 9.09mmol) and triethylamine (2.54ml, 18.18mmol). The mixture was heated at 60°C for 4h before addition of sodium azide (1.36g, 27.27mmol). Heating was continued at 60°C for a further 72h. The reaction mixture was cooled and partitioned between water (50ml) and ethyl acetate (100ml). The organic layer was separated and the solvent removed

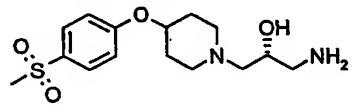
under reduced pressure. The residue was dissolved in THF (20ml) and water (2ml) and triphenylphosphine (5.90g, 22.72mmol) added. The mixture was heated at 60°C for 16h before dilution with ethyl acetate (100ml). The solution was washed with 1N HCl (50ml) and the aqueous layer was separated and adjusted to pH 11 with sodium hydroxide. The product was extracted with DCM (4x100ml). The organics were combined and dried sodium over sulfate and the solvent removed under reduced pressure. The residue was purified by flash chromatography to give the title compound as a pale yellow solid (1.10g).

MS (ESI) 310 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.56 (1H, d), 7.00 (1H, d), 6.85 (1H, dd), 4.42 (1H, septet), 3.73-3.67 (1H, m), 2.93-2.86 (1H, m), 2.86-2.78 (1H, m), 2.71-2.62 (2H, m), 2.61-2.55 (1H, m), 2.45-2.30 (3H, m), 2.06-1.96 (2H, m), 1.91-1.79 (2H, m).

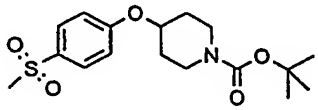
Preparation 25

(2*R*)-1-Amino-3-{4-[4-(methylsulfonyl)phenoxy]piperidin-1-yl}propan-2-ol



Prepared as described in Preparation 24 starting from 1-fluoro-4-(methylsulfonyl) benzene.

Step 1: *tert*-Butyl 4-[4-(methylsulfonyl)phenoxy]piperidine-1-carboxylate



^{1}H NMR δ ($CDCl_3$) 1.48 (9H, s), 1.74-1.82 (2H, m), 1.91-1.99 (2H, m), 3.04 (3H, s), 3.38 (2H, ddd), 3.69 (2H, ddd), 4.57-4.62 (1H, m), 7.02 (2H, d), 7.86 (2H, d).

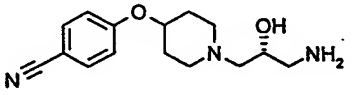
Step 2: (2*R*)-1-Amino-3-{4-[4-(methylsulfonyl)phenoxy]piperidin-1-yl}propan-2-ol

MS (ESI) 329 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.85 (2H, d), 7.01 (2H, d), 4.47 (1H, septet), 3.73-3.67 (1H, m), 3.03 (3H, s), 2.95-2.88 (1H, m), 2.86-2.78 (1H, m), 2.72-2.62 (2H, m), 2.61-2.55 (1H, m), 2.45-2.30 (3H, m), 2.08-1.98 (2H, m), 1.92-1.81 (2H, m).

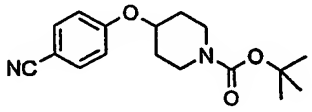
Preparation 26

4-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)benzonitrile



Prepared as described in Preparation 24 starting from 4-fluorobenzonitrile.

Step 1: *tert*-Butyl 4-(4-cyanophenoxy)piperidine-1-carboxylate



MS (ESI) 303 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.58 (2H, d), 6.95 (2H, d), 4.55 (1H, m), 3.69 (2H, ddd), 3.37 (2H, ddd), 1.97-1.90 (2H, m), 1.80-1.72 (2H, m), 1.47 (9H, s).

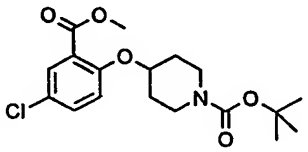
Step 2: 4-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)benzonitrile

MS (ESI) 276 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.57 (2H, d), 6.94 (2H, d), 4.46-4.41 (1H, m), 3.74-3.68 (1H, m), 2.94-2.88 (1H, m), 2.83 (1H, dd), 2.73-2.66 (1H, m), 2.64 (1H, dd), 2.61-2.55 (1H, m), 2.46-2.30 (3H, m), 2.07-1.97 (2H, m), 1.91-1.80 (2H, m).

Preparation 27

tert-Butyl 4-[4-chloro-2-(methoxycarbonyl)phenoxy]piperidine-1-carboxylate



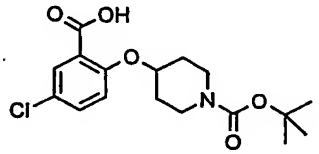
Diisopropylazodicarboxylate (5.2ml, 26.8mmol) was added dropwise to a solution of 5-chloro-2-hydroxy methylbenzoate (5.0g, 26.8mmol), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (5.4g, 26.8mmol) and triphenylphosphine (7.02g, 26.8mmol) in THF (200ml) at 0°C. The reaction mixture was allowed to warm to ambient temperature overnight. The solvent was removed under reduced pressure and the residue triturated with diethyl ether (200ml). The triphenylphosphineoxide was filtered off and the diethyl ether removed under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate:isohexane (1:9) to give the title compound as a brown oil (8.1g).

MS (ESI) 370 $(M+H)^+$

^{1}H NMR δ (DMSO) 1.47 (9H, s), 1.79-1.92 (4H, m), 3.45-3.54 (2H, m), 3.56-3.62 (2H, m), 3.89 (3H, s), 4.54-4.59 (1H, m), 6.92 (1H, d), 7.38 (1H, dd), 7.77 (1H, d).

Preparation 28

2-{[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-5-chlorobenzoic acid



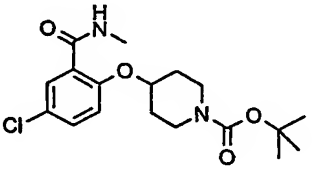
An aqueous solution of 2N sodium hydroxide (20ml) was added to a solution of *tert*-butyl 4-[4-chloro-2-(methoxycarbonyl) phenoxy]piperidine-1-carboxylate (8.1g, 22.0mmol) in tetrahydrofuran (70ml) at 45°C. The mixture was stirred vigorously for 3h then adjusted to pH 2 with 2N hydrochloric acid. The product was extracted with ethyl acetate and the organic layer washed repeatedly with water until the washings were pH 6. The organic layer was dried over magnesium sulfate and evaporated. The residue was azeotroped with toluene to give the title compound as a colourless solid (7.5g).

MS (ESI) 356 $(M+H)^+$

^{1}H NMR δ (DMSO) 1.47 (9H, s), 1.79-1.88 (2H, m), 2.03-2.11 (2H, m), 3.30 (2H, ddd), 3.77-3.85 (2H, m), 4.72 (1H, m), 7.02 (1H, d), 7.49 (1H, dd), 8.12 (1H, d), 10.91 (1H, s).

Preparation 29

4-(4-Chloro-2-methylcarbamoyl-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester



Bromo-tris-pyrrolidinophosphonium hexafluorophosphate (1.57g, 3.37mmol) was added to a vigorously stirred mixture of 2-{[1-(*tert*-butoxycarbonyl)piperidin-4-yl]oxy}-5-chlorobenzoic acid (1.00g, 2.81mmol) and 40% aq methylamine (2ml) in DCM (10ml). Stirring was continued for 30 min. before partitioning between 1N hydrochloric acid (10ml) and dichloromethane (10ml). The organic layer was separated and washed with

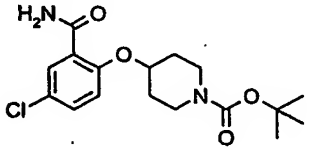
saturated sodium bicarbonate solution (20ml) and water (20ml), then dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate:isohexane (1:1) to give the title compound as a colourless solid (0.84g).

MS (ESI) 369 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.17 (1H, d), 7.75 (1H, s), 7.35 (1H, dd), 6.91 (1H, d), 4.58 (1H, tt), 3.81-3.71 (2H, m), 3.29 (2H, ddd), 3.00 (3H, d), 2.08-1.98 (2H, m), 1.82-1.71 (2H, m), 1.48 (9H, s).

Preparation 30

tert-Butyl 4-[2-(aminocarbonyl)-4-chlorophenoxy]piperidine-1-carboxylate



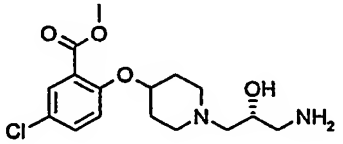
Prepared as described in Preparation 29 using aqueous ammonia.

MS (ESI) 355 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.18 (1H, d), 7.67-7.61 (1H, m), 7.40 (1H, dd), 6.94 (1H, d), 5.83-5.76 (1H, m), 4.61 (1H, m), 3.84-3.76 (2H, m), 3.26 (2H, ddd), 2.09-2.01 (2H, m), 1.82-1.73 (2H, m), 1.47 (9H, s).

Preparation 31

Methyl 2-({1-[(2*R*)-3-amino-2-hydroxypropyl]piperidin-4-yl}oxy)-5-chlorobenzoate



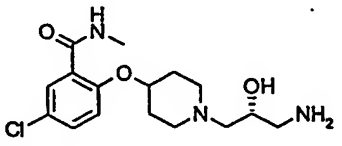
Prepared as described in Preparation 24, Step 2 from *tert*-butyl 4-[4-chloro-2-(methoxycarbonyl)phenoxy]piperidine-1-carboxylate.

MS (ESI) 343 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.75 (1H, d), 7.37 (1H, dd), 6.92 (1H, d), 4.46-4.39 (1H, m), 3.89 (3H, s), 3.72-3.66 (1H, m), 2.93-2.87 (1H, m), 2.81 (1H, dd), 2.69-2.55 (2H, m), 2.63 (1H, dd), 2.43-2.31 (3H, m), 2.00-1.84 (2H, m), 1.67-1.46 (2H, m).

Preparation 32

2-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)-5-chloro-*N*-methylbenzamide



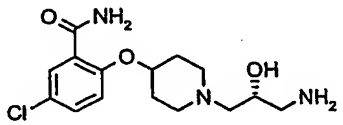
Prepared as described in Preparation 24, Step 2 from 4-(4-chloro-2-methylcarbamoyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester.

MS (ESI) 342 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.18 (1H, d), 7.88 (1H, s), 7.34 (1H, dd), 6.91 (1H, d), 4.54-4.48 (1H, m), 3.73-3.67 (1H, m), 3.01 (3H, d), 2.89-2.83 (1H, m), 2.83 (1H, dd), 2.68-2.56 (2H, m), 2.63 (1H, dd), 2.44 (1H, dd), 2.39-2.33 (1H, m), 2.34 (1H, dd), 2.13-2.03 (2H, m), 1.94-1.83 (2H, m).

Preparation 33

2-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)-5-chlorobenzamide



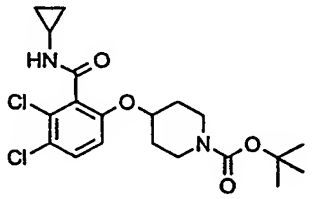
Prepared as described in Preparation 24, Step 2 from *tert*-butyl 4-[2-(aminocarbonyl)-4-chlorophenoxy]piperidine-1-carboxylate.

MS (ESI) 328 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.19 (1H, d), 7.75 (1H, s), 7.39 (1H, dd), 6.93 (1H, d), 5.85 (1H, s), 4.56-4.48 (1H, m), 3.73-3.67 (1H, m), 2.93-2.86 (1H, m), 2.83 (1H, dd), 2.73-2.66 (1H, m), 2.63 (1H, dd), 2.61-2.54 (1H, m), 2.44 (1H, dd), 2.37-2.30 (1H, m), 2.35 (1H, dd), 2.15-2.05 (2H, m), 1.90 (2H, dtd).

Preparation 34

tert-Butyl 4-{3,4-dichloro-2-[(cyclopropylamino)carbonyl]phenoxy}piperidine-1-carboxylate



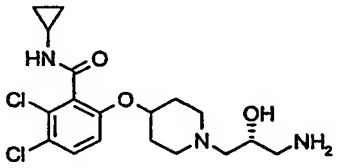
A solution of *tert*-butyl 4-[3,4-dichloro-2-(1H-imidazol-1-ylcarbonyl)phenoxy] piperidine-1-carboxylate (described in Preparation 11 step 1) (2.0g, 4.5mmol) in cyclopropylamine (12ml) was heated at 50°C for 14h. The solution was concentrated *in vacuo* then partitioned between ethyl acetate and 1N aqueous hydrochloric acid. The organics were dried over magnesium sulfate and concentrated *in vacuo*. Crystallization from dichloromethane:isohexane gave the title compound as a white solid (0.64g).

MS (ESI) 429/431 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.46 (1H, d), 7.56 (1H, d), 7.17 (1H, d), 4.68 (1H, m), 3.42-3.27 (4H, m), 2.74 (1H, m), 1.78 (2H, m), 1.55 (2H, m), 0.68 (2H, m), 0.44 (2H, m).

Preparation 35

6-{[1-(3-Amino-2-hydroxypropyl)piperidin-4-yl]oxy}-2,3-dichloro-*N*-cyclopropylbenzamide



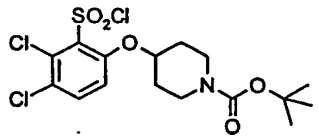
Prepared as described in Preparation 24, Step 2 following Preparation 34.

MS (ESI) 402 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.35 (1H, d), 6.78 (1H, d), 5.82 (1H, s), 4.40-4.33 (1H, m), 3.68 (1H, tt), 2.92-2.85 (2H, m), 2.85-2.77 (2H, m), 2.81 (1H, dd), 2.62 (1H, dd), 2.42-2.29 (3H, m), 2.00-1.89 (2H, m), 1.88-1.79 (2H, m), 0.89 (2H, td), 0.66-0.62 (2H, m).

Preparation 36

tert-Butyl 4-[3,4-dichloro-2-(chlorosulfonyl)phenoxy]piperidine-1-carboxylate



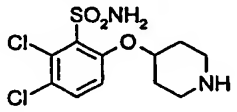
To a stirred solution of *tert*-butyl 4-[3,4-dichlorophenoxy]piperidine-1-carboxylate (10.0g, 28.9mmol) in dry THF (400ml) at –70°C under a nitrogen atmosphere was added dropwise *sec*-butyl lithium (26.7ml, 1.3M in cyclohexane). The solution was stirred a further 15min. at this temperature and then sulfur dioxide was bubbled through the mixture for 10min. The cooling bath was removed and the mixture warmed to room temperature over 1h. N-Chlorosuccinimide (4.63g, 35mmol) was added and the mixture stirred at room temperature for 72h. The solution was concentrated *in vacuo* and partitioned between ethyl acetate and 1N aqueous hydrochloric acid. The organic extracts were dried (magnesium sulphate) and concentrated. Chromatography on silica (ethyl acetate: isohexane/1:3) gave the title compound (2.40g)

MS (ESI) 445 $(M+H)^+$

^{1}H NMR δ (DMSO) 7.45 (1H, d), 7.03 (1H, d), 4.65 (1H, m), 3.59 (2H, m), 3.33 (3H, s), 1.66 (4H, m), 1.40 (9H, s).

Preparation 37

2,3-Dichloro-6-(piperidin-4-yloxy)benzenesulfonamide



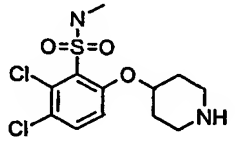
tert-Butyl-4-[3,4-dichloro-2-(chlorosulfonyl)phenoxy]piperidine-1-carboxylate (0.80g, 1.8mmol) was dissolved in 7N ammonia in methanol and stirred at room temperature for 20min. The solution was concentrated *in vacuo* and then azeotroped once with toluene. The residue was redissolved in dichloromethane:trifluoroacetic acid / 1:1 (20ml) and stirred at room temperature for 15 minutes. The solution was concentrated *in vacuo*, then partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The aqueous was reextracted with ethyl acetate (4 times), and the combined organics dried over anhydrous potassium carbonate. Concentration *in vacuo* afforded the title compound as a white powder (0.54g).

MS (ESI) 325/327 $(M+H)^+$

^{1}H NMR δ (DMSO) 7.74 (1H, d), 7.34 (1H, d), 4.66 (1H, m), 2.96 (2H, m), 2.55 (2H, m), 1.91 (2H, m), 1.63 (2H, m).

Preparation 38

2,3-Dichloro-*N*-methyl-6-(piperidin-4-yloxy)benzenesulfonamide



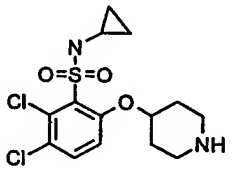
tert-Butyl 4-[3,4-dichloro-2-(chlorosulfonyl)phenoxy]piperidine-1-carboxylate (0.70g, 1.8mmol) was dissolved in 40% aqueous methylamine in water (10ml) and methanol (10ml) and stirred at room temperature for 30min. The solution was concentrated *in vacuo* and then azeotroped with toluene (4 times). The residue was redissolved in dichloromethane/trifluoroacetic acid (1:1) (20ml) and stirred at room temperature for 15 minutes. The solution was concentrated *in vacuo*, then partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The aqueous was reextracted with ethyl acetate (4 times), and the combined organics dried over anhydrous potassium carbonate. Concentration *in vacuo* afforded the title compound as a white powder (0.69g).

MS (ESI) 339/341 $(M+H)^+$

^{1}H NMR δ (DMSO) 7.76 (1H, d), 7.35 (1H, d), 4.64 (1H, m), 2.96 (2H, m), 2.54 (3H, s), 2.54 (2H, m), 1.90 (2H, m), 1.61 (2H, m).

Preparation 39

2,3-Dichloro-N-cyclopropyl-6-(piperidin-4-yloxy)benzenesulfonamide



tert-Butyl 4-[3,4-dichloro-2-(chlorosulfonyl)phenoxy]piperidine-1-carboxylate (0.70g, 1.8mmol) was dissolved in cyclopropylamine (8ml) and stirred at room temperature for 30min. The solution was concentrated *in vacuo* and then azeotroped with toluene (4 times). The residue was redissolved in dichloromethane: trifluoroacetic acid /

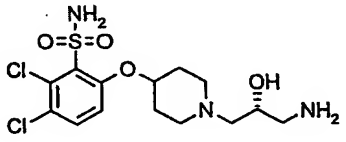
1:1 (20ml) and stirred at room temperature for 15min. The solution was concentrated *in vacuo*, then partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The aqueous was reextracted with ethyl acetate (4 times), and the combined organics dried over anhydrous potassium carbonate. Concentration *in vacuo* afforded the title compound as a white powder (0.70g).

MS (ESI) 365/367 $(M+H)^+$

^{1}H NMR δ (DMSO) 7.78 (1H, d), 7.36 (1H, d), 4.65 (1H, m), 2.97 (2H, m), 2.55 (2H, m), 2.27 (1H, m), 1.89 (2H, m), 1.63 (2H, m), 0.49 (4H, m) ;

Preparation 40

6-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)-2,3-dichlorobenzenesulfonamide

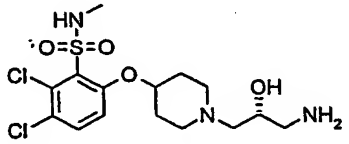


Prepared as described in Preparation 7 (Steps 2 and 3) following Preparation 37.

MS (ESI) 398/400 $(M+H)^+$

Preparation 41

6-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)-2,3-dichloro-*N*-methylbenzenesulfonamide

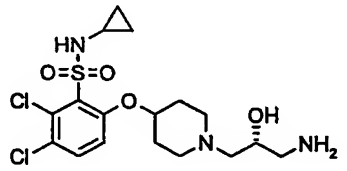


Prepared as described in Preparation 7 (Steps 2 and 3) following Preparation 38.

MS (ESI) 412/414 $(M+H)^+$

Preparation 42

6-({1-[(2*R*)-3-Amino-2-hydroxypropyl]piperidin-4-yl}oxy)-2,3-dichloro-*N*-cyclopropylbenzenesulfonamide

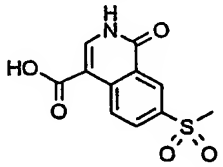


Prepared as described in Preparation 7 (Steps 2 and 3) following Preparation 39.

MS (ESI) 438/440 $(M+H)^+$

Preparation 43

7-(Methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



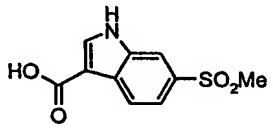
To a solution of sodium bicarbonate (500mg) and sodium sulfite (353mg) in 4ml of water at 0°C was added portionwise the 7-(chlorosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (see Preparation 16) (400mg). The reaction was warmed to room temperature and then heated at 80°C for 2h. The reaction was cooled to 0°C and acidified to pH~1 with concentrated hydrochloric acid. The suspension was diluted with 4ml of water and stirred for 15 minutes at 0°C then filtered under nitrogen. The solid was washed twice with water and was added to a degassed aqueous solution (3ml) of potassium hydrogen carbonate (280mg) at 45°C. Ethanol was then slowly added until the solution became slightly cloudy. Iodomethane (262µl) was then added and the reaction refluxed (45-50°C) for 5h. The reaction was concentrated under vacuum, extracted with ethyl acetate and the aqueous phase acidified with concentrated hydrochloric acid. The reaction was stirred at 0°C for 30 min. and the solid collected by filtration then recrystallised from acetone to yield the title compound as a white solid (325mg).

MS (ESI) 266 $(M-H)^-$

^{1}H NMR δ (DMSO) 12.97 (1H, bs), 12.19 (1H, d), 9.07 (1H, d), 8.70 (1H, d), 8.27 (1H, dd), 8.19 (1H, d), 3.30 (3H, s).

Preparation 44

6-(Methylsulphonyl)-1*H*-indole-3-carboxylic acid



Prepared as described in Preparation 43 following Preparation 16 using indole-3-carboxylic acid.

MS (ESI) 238 $(M-H)^-$

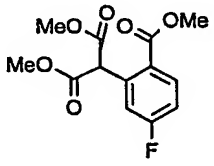
^{1}H NMR δ (DMSO) 12.34 (1H, bd s), 12.29 (1H, v bd s), 8.31 (1H, s), 8.21 (1H, d), 8.03 (1H, d), 7.69 (1H, dd), 3.20 (1H, d).

Preparation 45

6-Fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid

Prepared following literature procedures: *Liebigs Annalen der Chemie*, **1981**, *5*, 819-27 and *Chemical & Pharmaceutical Bulletin*, **1983**, *31*, 1277-82.

Step 1: Dimethyl [5-fluoro-2-(methoxycarbonyl)phenyl]malonate

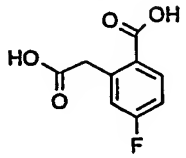


(Prepared according to US 5189168)

To a rapidly stirred suspension of 2-bromo-4-fluorobenzoic acid (4.5g) and copper(I) bromide (175mg) in 25ml of dimethylmalonate at 0°C was added portionwise sodium hydride (60% in mineral oil, 1.3g). After 10 min., the reaction warmed to room temperature and stirred for 30 minutes at room temperature then heated at 70°C for 2h. The solidified reaction was then diluted with water (80ml) and was extracted with diethyl ether (3x50ml). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3x100). The combined organic layers were dried over magnesium sulfate, filtered, concentrated under vacuum and the crude material recrystallised from diethyl ether/*iso*-hexane to yield the sub-title compound as a white solid (1.9g).

^{1}H NMR δ (DMSO) 13.36 (1H, bs), 8.05 (1H, dd), 7.35 (1H, ddd), 7.14 (1H, dd), 5.08 (1H, s), 3.70 (6H, s).

Step 2: 2-(Carboxymethyl)-4-fluorobenzoic acid

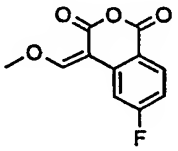


A suspension of dimethyl [5-fluoro-2-(methoxycarbonyl)phenyl]malonate (1.80g) in concentrated hydrochloric acid (25ml) was heated at 110°C for 48h. The reaction was cooled and the sub-title compound collected as a white solid by filtration (1.50g).

MS (ESI) 197 $(M-H)^-$

^{1}H NMR δ (DMSO) 7.97 (1H, dd), 7.24 (1H, dd), 7.20 (1H, dd), 3.96 (2H, s).

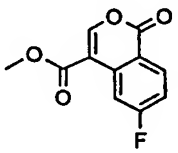
Step 3: (4*Z*)-6-Fluoro-4-(methoxymethylene)-1*H*-isochromene-1,3(4*H*)-dione



2-(Carboxymethyl)-4-fluorobenzoic acid (1.40g) in a mixture of acetic acid (3ml) and trimethylorthoformate (1ml) was heated at 110°C for 3h. During this time the methyl acetate generated was distilled off. When finished, the reaction was cooled to 0°C. The white solid was collected by filtration and was washed with cold water and methanol (1.32g).

MS (ESI) 207 $(M-Me)^-$

Step 4: Methyl 6-fluoro-1-oxo-1*H*-isochromene-4-carboxylate



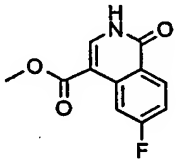
To a suspension of (4*Z*)-6-fluoro-4-(methoxymethylene)-1*H*-isochromene-1,3(4*H*)-dione (1.30g) in methanol (20ml) was slowly added sulfuric acid (1.5ml). The mixture was heated at 40-50°C for 3h. As the reaction proceeded the sub-title compound crystallized

out. The reaction was cooled to room temperature and a white solid was collected by filtration and washed with cold methanol.

MS (ESI) 222 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.49 (1H, s), 8.30 (1H, dd), 8.25 (1H, dd), 7.56 (1H, td), 3.87 (3H, s).

Step 5: Methyl 6-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylate

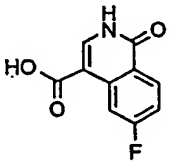


A mixture of methyl 6-fluoro-1-oxo-1*H*-isochromene-4-carboxylate (1.53g) and ammonium acetate (2.5g) in 4ml of glacial acetic acid was heated at 80°C for 16h. The reaction was cooled to 40°C, diluted with 8ml of water and the solid collected by filtration (1.38g).

MS (ESI) 220 $(M-H)^-$

^{1}H NMR δ (DMSO) 12.00 (1H, s), 8.46 (1H, dd), 8.32 (1H, dd), 8.10 (1H, s), 7.44 (1H, td), 3.83 (3H, s).

Step 6: 6-Fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



To a solution of methyl 6-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (1.3g) in methanol (3ml) was added a aqueous solution (3ml) of sodium hydroxide (1g) and the reaction mixture was heated at 80°C for 3h. The reaction was cooled to 20°C and carefully acidified with concentrated hydrochloric acid. The white precipitate was isolated by filtration, washed with water and methanol to yield the title compound (1.16g)

MS (ESI) 206 $(M-H)^-$

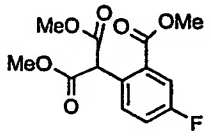
^{1}H NMR δ (DMSO) 12.85 (1H, s), 11.91 (1H, d), 8.58 (1H, dd), 8.31 (1H, dd), 8.09 (1H, d), 7.41 (1H, td).

Preparation 46

7-Fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid

Prepared following literature procedures: *Liebigs Annalen der Chemie*, **1981**, *5*, 819-27 and *Chemical & Pharmaceutical Bulletin*, **1983**, *31*, 1277-82.

Step 1: Dimethyl [4-fluoro-2-(methoxycarbonyl)phenyl]malonate

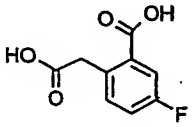


Prepared as described in Preparation 45, Step1 using 2-bromo-5-fluorobenzoic acid.

MS (ESI) 269/237 $(M-H)^-$

^{1}H NMR δ (DMSO) 7.70 (1H, dd), 7.49 (1H, td), 7.39 (1H, dd), 5.71 (1H, s), 3.68 (6H, s).

Step 2: 2-(Carboxymethyl)-5-fluorobenzoic acid

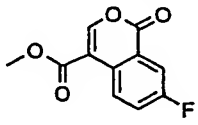


Prepared as described in Preparation 45, Step 2 using dimethyl [4-fluoro-2-(methoxycarbonyl)phenyl]malonate.

MS (ESI) 197 $(M-H)^-$

^{1}H NMR δ (DMSO) 7.81-7.74 (1H, m), 7.62 (1H, dd), 7.41-7.35 (1H, m), 3.92 (2H, s).

Step 3: Methyl 7-fluoro-1-oxo-1*H*-isochromene-4-carboxylate

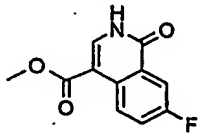


Prepared as described in Preparation 45, Steps 3 and 4 using 2-(carboxymethyl)-5-fluorobenzoic acid.

MS (ESI) 223 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.60 (1H, dd), 8.42 (1H, s), 7.95 (1H, dd), 7.86 (1H, ddd), 3.87 (3H, s).

Step 4: Methyl 7-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylate

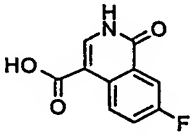


Prepared as described in Preparation 45, Step 5 using methyl 7-fluoro-1-oxo-1*H*-isochromene-4-carboxylate.

MS (ESI) 221 $(M-H)^-$

^{1}H NMR δ (DMSO) 12.04 (1H, s), 8.82 (1H, dd), 8.03 (1H, s), 7.91 (1H, dd), 7.73 (1H, td), 3.83 (3H, s).

Step 5: 7-Fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



Prepared as described in Preparation 45, Step 6 using methyl 7-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylate.

MS (ESI) 206 $(M-H)^-$

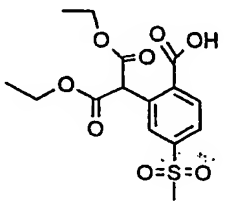
^{1}H NMR δ (DMSO) 12.81 (1H, s), 12.00 (1H, d), 8.93 (1H, dd), 8.02 (1H, d), 7.90 (1H, dd), 7.71 (1H, td).

Preparation 47

6-(Methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid

Prepared following literature procedures: *Liebigs Annalen der Chemie*, **1981**, *5*, 819-27 and *Chemical & Pharmaceutical Bulletin*, **1983**, *31*, 1277-82.

Step 1: 2-[2-Ethoxy-1-(ethoxycarbonyl)-2-oxoethyl]-4-(methylsulfonyl)benzoic acid



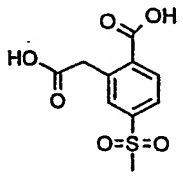
Prepared following literature procedure: *Journal of Organic Chemistry*, **1998**, *63*, 4116-4119.

To a very rapidly stirred suspension of 2-chloro-4-(methylsulfonyl)benzoic acid (10.0g) and copper(I) bromide (1.0g) in 50ml of diethylmalonate at 20°C was added portionwise sodium ethoxide (10.0g). The reaction was stirred for 30 min. at room temperature then heated at 90°C for 36h. The slurry was diluted with water (200ml), aqueous ammonia was added (3ml) and the mixture extracted with diethyl ether (3x100ml). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3x100ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum.

MS (ESI) 357/311 $(M-H)^-$

^1H NMR δ (CD_3OD) 8.28 (1H, d), 8.06 (1H, dd), 7.99 (1H, d), 5.78 (1H, s), 4.20 (4H, q), 3.19 (3H, s), 1.28 (6H, t).

Step 2: 2-(Carboxymethyl)-4-(methylsulfonyl)benzoic acid



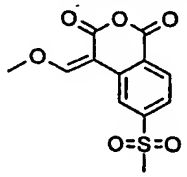
Prepared following literature procedure: *Journal of Organic Chemistry*, **1998**, *63*, 4116-4119.

The crude material of Step 1 was dissolved in methanol (200ml) and a solution (200ml) of sodium hydroxide (13g) slowly added. The reaction was stirred at room temperature for 3h. The methanol was removed under vacuum. The aqueous layer was extracted with diethyl ether (3x100ml), acidified with concentrated hydrochloric acid, saturated with sodium chloride and extracted with ethyl acetate (3x100ml). The combined organic layers were dried over magnesium sulfate, filtered, concentrated to one third volume and heated at 65°C for 3h to complete decarboxylation. A solid formed which was collected by filtration (7.1g).

MS (ESI) 257/213 $(M-H)^-$

^1H NMR δ (DMSO) 8.10 (1H, d), 7.95 (1H, d), 7.93 (1H, dd), 4.07 (2H, s), 3.28 (3H, s).

Step 3: (4*Z*)-4-(methoxymethylene)-6-(methylsulfonyl)-1*H*-isochromene-1,3(4*H*)-dione

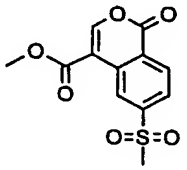


Prepared as described in Preparation 45, Step 3 using 2-(carboxymethyl)-4-(methylsulfonyl)benzoic acid.

MS (ESI) 267 $(M\text{-}Me)^-$

^{1}H NMR δ (DMSO) 8.68 (1H, d), 8.32 (1H, d), 8.31 (1H, s), 7.98 (1H, dd), 4.36 (3H, s), 3.46 (3H, s).

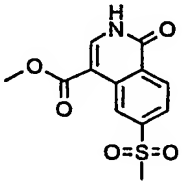
Step 4: Methyl 6-(methylsulfonyl)-1-oxo-1*H*-isochromene-4-carboxylate



Prepared as described in Preparation 45, Step 4 using (4*Z*)-4-(methoxymethylene)-6-(methylsulfonyl)-1*H*-isochromene-1,3(4*H*)-dione.

^{1}H NMR δ (DMSO) 9.08 (1H, d), 8.56 (1H, s), 8.44 (1H, d), 8.18 (1H, dd), 3.89 (3H, s), 3.34 (3H, s).

Step 5: Methyl 6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate

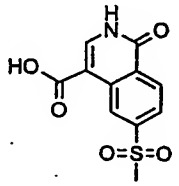


Prepared as described in Preparation 45, Step 5 using methyl 6-(methylsulfonyl)-1-oxo-1*H*-isochromene-4-carboxylate.

MS (ESI) 280 $(M\text{-}H)^-$

^{1}H NMR δ (DMSO) 12.23 (1H, s), 9.35 (1H, d), 8.47 (1H, d), 8.17 (1H, s), 8.06 (1H, dd), 3.86 (3H, s), 3.78 (3H, s).

Step 6: 6-(Methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



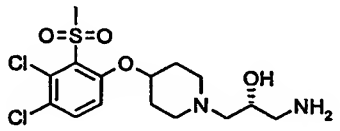
Prepared as described in Preparation 45, Step 6 using methyl 6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate.

MS (ESI) 266 $(M-H)^-$

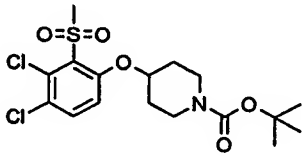
^1H NMR δ (DMSO) 12.99 (1H, s), 12.14 (1H, d), 9.45 (1H, d), 8.46 (1H, d), 8.15 (1H, d), 8.04 (1H, dd), 3.30 (3H, s).

Preparation 48

(2*R*)-1-Amino-3-{4-[3,4-dichloro-2-(methylsulfonyl)phenoxy]piperidin-1-yl}propan-2-ol



Step 1: *tert*-butyl 4-[3,4-dichloro-2-(methylsulfonyl)phenoxy]piperidine-1-carboxylate



To a stirred solution of *tert*-butyl 4-[3,4-dichlorophenoxy]piperidine-1-carboxylate (10.0g, 28.9mmol) in dry THF (400ml) at –70°C under a nitrogen atmosphere was added dropwise *sec*-butyl lithium (26.7ml, 1.3M in cyclohexane). The solution was stirred a further 15min. at this temperature and then was treated with dimethyldisulfide (3.9ml, 43mmol). The solution was stirred at this temperature for 30 min. and then the cooling bath removed and the mixture stirred vigorously whilst warming to –30°C over 30 min. Saturated aqueous ammonium chloride solution (5ml) was added and the mixture concentrated to *ca* 30ml volume and partitioned between water and ethyl acetate. The organic extracts were dried over magnesium sulphate and concentrated. Treatment of the crude residue with *meta*-chloroperbenzoic acid (13.3g, 57-86%) in dichloromethane (200ml) at room temperature for 14h gave the crude sulfone. The solution was shaken with

sodium metabisulfite solution, then the organics dried over magnesium sulfate and concentrated *in vacuo*. Chromatography on silica (ethyl acetate: isohexane) gave the subtitle compound (0.65g)

MS (ESI) 424/426 $(M+H)^+$

^{1}H NMR δ (DMSO) 7.88 (1H, d), 7.42 (1H, d), 4.92 (1H, m), 3.52 (2H, m), 3.32 (3H, s), 3.36-3.27 (2H, m), 1.90 (2H, m), 1.69 (2H, m), 1.40 (9H, s).

Step 2: (2*R*)-1-Amino-3-{4-[3,4-dichloro-2-(methylsulfonyl)phenoxy]piperidin-1-yl}propan-2-ol

Prepared as described in Preparation 24, Step 2 from *tert*-butyl 4-[3,4-dichloro-2-(methylsulfonyl)phenoxy]piperidine-1-carboxylate.

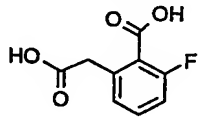
MS (ESI) 397/399 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.60 (1H, d), 6.94 (1H, d), 4.60-4.53 (1H, m), 3.73-3.67 (1H, m), 3.33 (3H, s), 3.02-2.96 (1H, m), 2.81 (1H, dd), 2.79-2.73 (1H, m), 2.64-2.56 (1H, m), 2.63 (1H, dd), 2.43-2.32 (3H, m), 2.11-1.91 (4H, m)

Preparation 49

8-Fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid

Step 1: 2-(Carboxymethyl)-6-fluorobenzoic acid

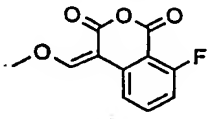


Prepared as described in Preparation 45, Step 1 and 2 using 2-bromo-6-fluorobenzoic acid.

MS (ESI) 197 $(M-H)^-$

^{1}H NMR δ (DMSO) 7.46 (1H, td), 7.20 (1H, dd), 7.18 (1H, d), 3.77 (2H, s).

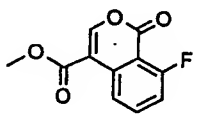
Step 2: (4*Z*)-8-Fluoro-4-(methoxymethylene)-1*H*-isochromene-1,3(4*H*)-dione



Prepared as described in Preparation 45, Step 3 using 2-(carboxymethyl)-6-fluorobenzoic acid.

MS (ESI) 207 $(M-Me)^-$

Step 3: Methyl 8-fluoro-1-oxo-1*H*-isochromene-4-carboxylate

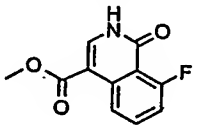


Prepared as described in Preparation 45, Step 4 using (4*Z*)-8-fluoro-4-(methoxymethylene)-1*H*-isochromene-1,3(4*H*)-dione.

MS (ESI) 222 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.42 (1H, s), 8.34 (1H, d), 7.96 (1H, td), 7.50 (1H, dd), 3.86 (2H, s).

Step 4: Methyl 8-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylate

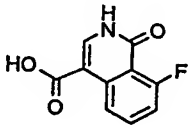


Prepared as described in Preparation 45, Step 5 using methyl 8-fluoro-1-oxo-1*H*-isochromene-4-carboxylate

MS (ESI) 220 $(M-H)^-$

^{1}H NMR δ (DMSO) 11.86 (1H, s), 8.57 (1H, d), 8.03 (1H, s), 7.80 (1H, td), 7.30 (1H, dd), 3.82 (3H, s).

Step 5: 8-Fuoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid



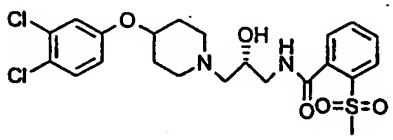
Prepared as described in Preparation 45, Step 6 using methyl 8-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylate.

MS (ESI) 206 $(M-H)^-$

^{1}H NMR δ (DMSO) 12.75 (19H, s), 11.76 (19H, d), 8.69 (22H, d), 8.02 (23H, d), 7.78 (24H, td), 7.29 (22H, dd).

Example 1

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylsulfonyl)benzamide.



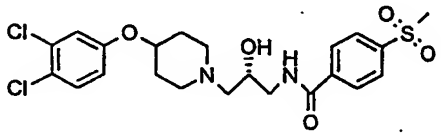
A mixture of 2-(methylsulphonyl)benzoic acid (0.063g), (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and *N,N*-diisopropylethylamine (0.1ml) in dry dimethylformamide (3ml) was cooled to 0°C with stirring. 2-(1H-9-Azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.13g) was added and the mixture was stirred at 0°C for 1-2h. Saturated sodium bicarbonate solution (10ml) was added. The mixture was extracted with ethyl acetate. The organic layer was separated and washed with brine and dried over sodium sulphate. The mixture was filtered and the solvent was evaporated. The resulting oil was purified by normal phase chromatography using methanol/dichloromethane as eluent, and by reverse phase HPLC using acetonitrile and 0.1% aqueous ammonium acetate as eluent, to give the title compound as a white solid (0.055g).

MS (APCI) 501/503 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.57 (1H, t), 7.96 (1H, dd), 7.78 (1H, td), 7.69 (1H, td), 7.57 (1H, dd), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.48-4.37 (1H, m), 3.85-3.74 (1H, m), 3.40-3.25 (1H, m), 3.37 (3H, s), 3.26-3.13 (1H, m), 2.83-2.69 (2H, m), 2.44 (1H, dd), 2.37-2.26 (3H, m), 1.95-1.84 (2H, m), 1.65-1.50 (2H, m).

Example 2

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(methylsulfonyl)benzamide



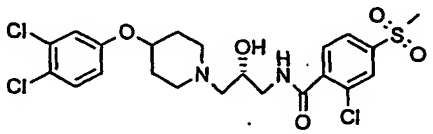
Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 4-(methylsulphonyl)benzoic acid (0.063g). Title compound obtained as white solid (0.038g).

MS (APCI) 501/503 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.69 (1H, t), 8.05 (4H, dd), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.76 (1H, brs), 4.43 (1H, mult), 3.86-3.78 (1H, m), 3.43 (1H, dt), 3.26 (3H, s), 3.20 (1H, dd), 2.79-2.67 (2H, m), 2.41-2.24 (4H, m), 1.95-1.85 (2H, m), 1.66-1.54 (2H, m).

Example 3

2-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(methylsulfonyl)benzamide



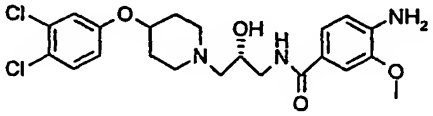
Prepared as described in Example 1 using (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 3-(methylsulfonyl)benzoic acid (0.074g). Title compound obtained as white solid (0.033g).

MS (APCI) 535/537 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.60 (1H, t), 8.03 (1H, d), 7.93 (1H, dd), 7.70 (1H, d), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.70 (1H, brs), 4.47-4.39 (1H, m), 3.82-3.74 (1H, m), 3.41-3.31 (1H, m), 3.29 (3H, s), 3.23-3.15 (1H, m), 2.80-2.69 (2H, m), 2.44-2.25 (4H, m), 1.96-1.86 (2H, m), 1.65-1.54 (2H, m).

Example 4

4-Amino-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-methoxybenzamide



Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 4-amino-3-methoxybenzoic acid (0.052g). Title compound obtained as white solid (0.053g).

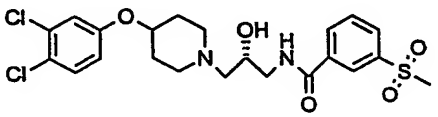
MS (APCI) 468/470 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.05 (1H, t), 7.49 (1H, d), 7.31-7.27 (2H, m), 7.25 (1H, d), 6.98 (1H, dd), 6.60 (1H, d), 5.23 (2H, s), 4.74 (1H, brs), 4.47-4.38 (1H, m), 3.80 (3H, s),

3.81-3.73 (1H, m), 3.38-3.30 (1H, m), 3.18-3.09 (1H, m), 2.80-2.65 (2H, m), 2.36 (2H, dd), 2.32-2.22 (2H, m), 1.95-1.86 (2H, m), 1.66-1.54 (2H, m).

Example 5

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(methylsulfonyl)benzamide



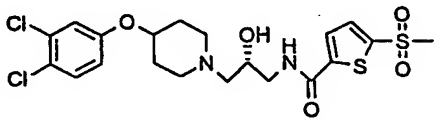
Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 3-(methylsulfonyl)benzoic acid (0.063g). Title compound obtained as white solid (0.017g).

MS (APCI) 501/503 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.74 (1H, t), 8.39 (1H, t), 8.18 (1H, dt), 8.07 (1H, ddt), 7.76 (1H, t), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.77 (1H, brs), 4.47-4.39 (1H, m), 3.86-3.78 (1H, m), 3.45 (1H, dt), 3.26 (3H, s), 3.24-3.14 (1H, m), 2.80-2.66 (2H, m), 2.41-2.24 (4H, m), 1.95-1.86 (2H, m), 1.65-1.54 (2H, m).

Example 6

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(methylsulfonyl)thiophene-2-carboxamide.



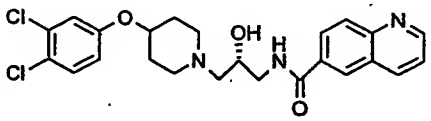
Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 5-(methylsulfonyl)thiophene-2-carboxylic acid (0.065g). Title compound obtained as white solid (0.039g).

MS (APCI) 507/509 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.85 (1H, t), 7.84 (2H, dd), 7.49 (1H, d), 7.26 (1H, d), 6.98 (1H, dd), 4.80 (1H,brs), 4.47-4.39 (1H, m), 3.83-3.75 (1H, m), 3.45-3.38 (1H, m), 3.38 (3H, s), 3.18-3.09 (1H, m), 2.79-2.66 (2H, m), 2.37-2.22 (4H, m), 1.95-1.85 (2H, m), 1.65-1.53 (2H, m).

Example 7

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoline-6-carboxamide



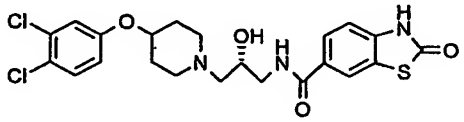
Prepared as described in Example from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and quinoline-6-carboxylic acid (0.054g). Title compound obtained as white solid (0.032g).

MS (APCI) 474/476 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.98 (1H, dd), 8.68 (1H, t), 8.52 (1H, d), 8.47 (1H, dd), 8.19 (1H, dd), 8.08 (1H, d), 7.61 (1H, dd), 7.49 (1H, d), 7.24 (1H, d), 6.97 (1H, dd), 4.78 (1H, brs), 4.48-4.39 (1H, m), 3.90-3.82 (1H, m), 3.46 (1H, dt), 3.31-3.23 (1H, m), 2.82-2.70 (2H, m), 2.45-2.25 (4H, m), 1.96-1.87 (2H, m), 1.67-1.55 (2H, m).

Example 8

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-2,3-dihydro-1,3-benzothiazole-6-carboxamide acetate salt



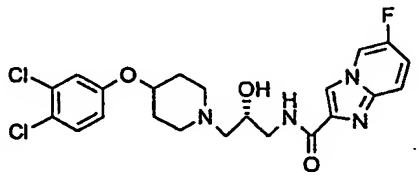
Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 2-oxo-2,3-dihydro-1,3-benzothiazole-6-carboxylic acid (0.061g). Title compound obtained as acetate salt, a white solid (0.10g).

MS (APCI) 496/498 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.36 (1H, t), 8.05 (1H, d), 7.78 (1H, dd), 7.49 (1H, d), 7.25 (1H, d), 7.15 (1H, d), 6.98 (1H, dd), 4.47-4.40 (1H, m), 3.80 (1H, quintet), 3.38 (1H, dt), 3.22-3.14 (1H, m), 2.80-2.67 (2H, m), 2.41-2.25 (4H, m), 1.95-1.86 (2H, m), 1.91 (3H, s), 1.66-1.54 (2H, m).

Example 9

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-fluoroimidazo[1,2-*a*]pyridine-2-carboxamide



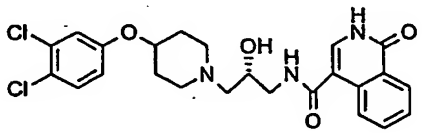
Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 6-fluoroimidazo[1,2-a]pyridine-2-carboxylic acid (0.056g). Title compound obtained as white solid (0.076g).

MS (APCI) 481/482 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.80-8.78 (1H, m), 8.63 (1H, t), 8.33 (1H, s), 7.68 (1H, dd), 7.50 (1H, d), 7.52-7.44 (1H, m), 7.28 (1H, d), 7.00 (1H, dd), 4.89 (1H, s), 4.52-4.44 (1H, m), 3.83-3.74 (1H, m), 3.44-3.28 (2H, m), 2.83-2.66 (2H, m), 2.44-2.23 (4H, m), 2.02-1.90 (2H, m), 1.82-1.72 (2H, m).

Example 10

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



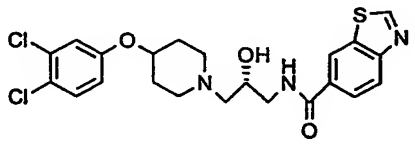
Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (0.059g). Title compound obtained as white solid (0.047g).

MS (APCI) 490/492 $(M+H)^+$

^{1}H NMR δ (DMSO) 11.59 (1H, d), 8.33 (1H, t), 8.22 (2H, dd), 7.73 (1H, t), 7.54-7.48 (3H, m), 7.26 (1H, d), 6.98 (1H, dd), 4.79 (1H, s), 4.48-4.40 (1H, m), 3.85-3.76 (1H, m), 3.43-3.31 (1H, m), 3.14 (1H, quintet), 2.83-2.69 (2H, m), 2.45-2.25 (4H, m), 1.96-1.87 (2H, m), 1.67-1.55 (2H, m).

Example 11

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,3-benzothiazole-6-carboxamide



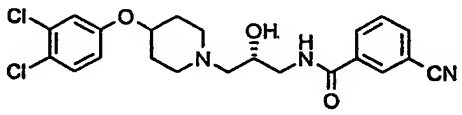
Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.1g) and 1,3-benzothiazole-6-carboxylic acid (0.056g). Title compound obtained as white solid (0.066g).

MS (APCI) 480/482 $(M+H)^+$

^{1}H NMR δ (DMSO) 9.54 (1H, s), 8.67 (1H, d), 8.60 (1H, t), 8.15 (1H, d), 8.02 (1H, dd), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.78 (1H, brs), 4.47-4.39 (1H, m), 3.87-3.79 (1H, m), 3.44 (1H, dt), 3.23 (1H, quintet), 2.82-2.68 (2H, m), 2.40 (1H, dd), 2.37-2.23 (3H, m), 1.96-1.86 (2H, m), 1.66-1.54 (2H, m).

Example 12

3-Cyano-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



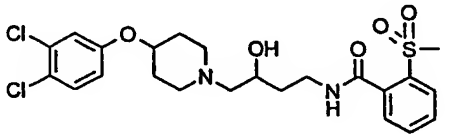
Prepared as described in Example 1 from (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.2g) and 3-cyanobenzoic acid (0.092g). Title compound obtained as white solid (0.050g).

MS (APCI) 448/450 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.10 (1H, s), 7.79 (1H, d), 7.58 (1H, t), 7.31 (1H, d), 7.00 (1H, d), 6.80 (1H, t), 6.75 (1H, dd), 4.38-4.25 (1H, m), 4.00-3.87 (1H, m), 3.81-3.68 (1H, m), 3.36 (1H, dt), 2.98-2.85 (1H, m), 2.75-2.63 (1H, m), 2.63-2.53 (1H, m), 2.48 (1H, dd), 2.37 (1H, d), 2.32 (2H, t), 2.07-1.90 (2H, m), 1.90-1.73 (2H, m).

Example 13

N-{4-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-3-hydroxybutyl}-2-(methylsulfonyl)benzamide



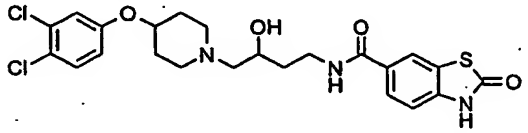
Prepared as described in Example 1 from 4-amino-1-[4-(3,4-dichlorophenoxy)piperidin-1-yl]butan-2-ol (0.26g) and 2-(methylsulphonyl)benzoic acid (0.156g). The title compound was obtained as a white solid (0.170g).

MS (APCI) 515/517 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.09 (1H, dd), 7.65 (1H, dd), 7.59 (1H, td), 7.53 (1H, dd), 7.31 (1H, d), 6.99 (1H, d), 6.74 (1H, dd), 6.74 (1H, dd), 4.32-4.23 (1H, m), 3.92-3.83 (1H, m), 3.83-3.74 (1H, m), 3.57-3.46 (1H, m), 3.37 (3H, s), 2.94-2.85 (1H, m), 2.70-2.60 (1H, m), 2.60-2.50 (1H, m), 2.40 (1H, dd), 2.35 (1H, dd), 2.32-2.23 (1H, m), 2.01-1.89 (2H, m), 1.88-1.69 (2H, m), 1.67-1.55 (2H, m).

Example 14

N-{4-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-3-hydroxybutyl}-2-oxo-2,3-dihydro-1,3-benzothiazole-6-carboxamide



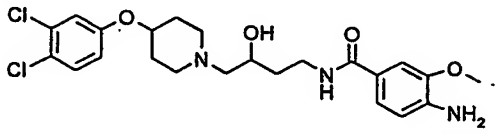
Prepared as described in Example 1 from 4-amino-1-[4-(3,4-dichlorophenoxy)piperidin-1-yl]butan-2-ol (0.26g) and 2-oxo-2,3-dihydro-1,3-benzothiazole-6-carboxylic acid (0.152g). Title compound obtained as a white solid (0.105g).

MS (APCI) 510/512 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.88 (1H, d), 7.71 (1H, dd), 7.48-7.39 (1H, m), 7.31 (1H, d), 7.13 (1H, d), 7.00 (1H, d), 6.76 (1H, dd), 4.36-4.27 (1H, m), 3.93-3.83 (2H, m), 3.49-3.38 (1H, m), 2.97-2.87 (1H, m), 2.73-2.53 (2H, m), 2.46-2.32 (2H, m), 2.36-2.27 (1H, m), 2.06-1.91 (2H, m), 1.90-1.75 (3H, m), 1.66-1.53 (1H, m).

Example 15

4-Amino-*N*-{4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-3-hydroxybutyl}-3-methoxybenzamide



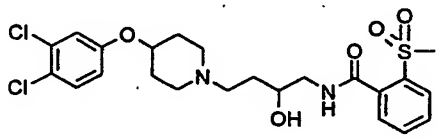
Prepared as described in Example 1 from 4-amino-1-[4-(3,4-dichlorophenoxy)piperidin-1-yl]butan-2-ol (0.26g) and 4-amino-3-methoxybenzoic acid (0.130g). Title compound obtained as white solid (0.080g).

MS (APCI) 482/484 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.39 (1H, d), 7.31 (1H, d), 7.15 (1H, dd), 7.04 (1H, bs), 7.00 (1H, d), 6.75 (1H, dd), 6.65 (1H, d), 4.29 (1H, septet), 4.08 (2H, bs), 3.90 (3H, s), 3.89-3.75 (2H, m), 3.49-3.36 (1H, m), 2.96-2.85 (1H, m), 2.73-2.61 (1H, m), 2.61-2.50 (1H, m), 2.44-2.34 (2H, m), 2.35-2.23 (1H, m), 2.07-1.90 (2H, m), 1.90-1.71 (2H, m), 1.70-1.48 (2H, m).

Example 16

N-{4-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxybutyl}-2-(methylsulfonyl)benzamide



Prepared as described in Example 1 from 1-amino-4-[4-(3,4-dichlorophenoxy)piperidin-1-yl]butan-2-ol (0.2g) and 2-(methylsulphonyl)benzoic acid (0.12g). Title compound obtained as white solid (0.090g).

MS (APCI) 515/517 $(M+H)^+$

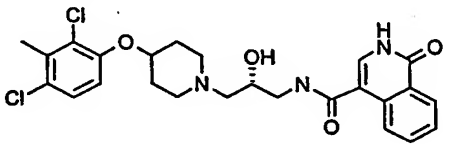
^{1}H NMR δ ($CDCl_3$) 8.10 (1H, d), 7.67 (1H, td), 7.61 (1H, td), 7.55 (1H, dd), 7.30 (1H, d), 6.98 (1H, d), 6.73 (1H, dd), 6.61 (1H, t), 4.33-4.23 (1H, m), 4.06 (1H, octet), 3.70 (1H, ddd), 3.36-3.29 (1H, m), 3.37 (3H, s), 2.97-2.82 (1H, m), 2.78-2.68 (1H, m), 2.64 (1H, dt), 2.60-2.47 (2H, m), 2.38-2.22 (1H, m), 2.02-1.41 (6H, m).

The compounds of Examples 17 and 18 were prepared in a similar way to Example 1 following Preparation 13 starting from 4-(2,4-dichloro-3-methylphenoxy)piperidine

(WO 00/58305, WO 01/77101).

Example 17

N-{(2R)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



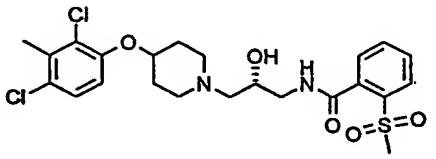
Prepared as described in Example 1 following Preparation 13.

MS (APCI) 504/506 $(M+H)^+$

^{1}H NMR δ (DMSO) 11.58 (1H, s), 8.31 (1H, t), 8.22 (2H, d), 7.72 (1H, t), 7.56-7.48 (2H, m), 7.35 (1H, d), 7.10 (1H, d), 4.80-4.70 (1H, m), 4.53-4.44 (1H, m), 3.85-3.75 (1H, m), 3.39 (1H, dt), 3.15 (1H, quintet), 2.78-2.64 (2H, m), 2.40 (3H, s), 2.39-2.27 (4H, m), 1.96-1.83 (2H, m), 1.74-1.61 (2H, m).

Example 18

N-{(2R)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylsulfonyl)benzamide



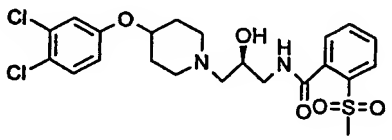
Prepared as described in Example 1 following Preparation 13.

MS (APCI) 515/517 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.10 (1H, dd), 7.67 (1H, t), 7.62 (1H, t), 7.54 (1H, dd), 7.19 (1H, d), 6.74 (1H, d), 6.55 (1H, t), 4.41- 4.27 (1H, m), 4.03-3.89 (1H, m), 3.68 (1H, ddd), 3.44 (1H, dt), 3.36 (3H, s), 3.00-2.87 (1H, m), 2.80-2.66 (1H, m), 2.63-2.51 (2H, m), 2.51-2.42 (1H, m), 2.47 (3H, s), 2.42-2.29 (1H, m), 2.03-1.76 (4H, m).

Example 19

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylsulfonyl)benzamide



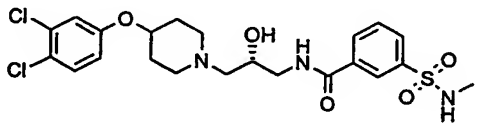
Prepared as described in Example 1 following Preparation 14.

MS (APCI) 501/503 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.10 (1H, dd), 7.68 (1H, td), 7.62 (1H, td), 7.54 (1H, dd), 7.31 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 6.53 (1H, t), 4.35-4.22 (1H, m), 4.04-3.91 (1H, m), 3.68 (1H, ddd), 3.45 (1H, dt), 3.36 (3H, s), 2.98-2.85 (1H, m), 2.80-2.66 (1H, m), 2.65-2.52 (2H, m), 2.46 (1H, dd), 2.41-2.28 (1H, m), 2.04-1.88 (2H, m), 1.87-1.67 (2H, m).

Example 20

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-[(methylamino)sulfonyl]benzamide



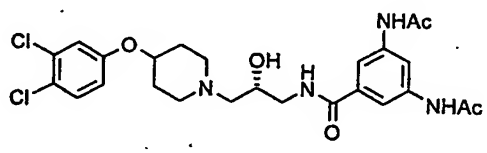
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 516/518 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.25 (1H, s), 7.99 (1H, d), 7.95 (1H, d), 7.55 (1H, t), 7.41 (1H, t), 7.31 (1H, d), 7.00 (1H, d), 6.75 (1H, dd), 4.95 (1H, s), 4.36-4.25 (1H, m), 4.16-4.05 (1H, m), 3.75 (1H, ddd), 3.31 (1H, ddd), 3.02-2.90 (1H, m), 2.74-2.56 (2H, m), 2.68 (3H, s), 2.51 (1H, dd), 2.37-2.26 (1H, m), 2.37 (1H, dd), 2.07-1.91 (2H, m), 1.91-1.72 (2H, m).

Example 21

3,5-Bis(acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



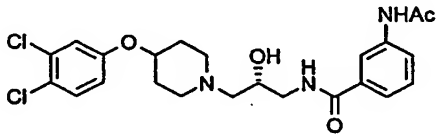
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 537/539 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 9.00 (2H, s), 7.86 (1H, s), 7.66 (2H, s), 7.50 (1H, s), 7.31 (1H, d), 6.99 (1H, d), 6.74 (1H, dd), 4.42-4.27 (1H, m), 4.19-4.03 (1H, m), 3.63-3.46 (1H, m), 3.42-3.26 (1H, m), 3.05-2.91 (1H, m), 2.91-2.74 (1H, m), 2.75-2.54 (4H, m), 2.17-1.96 (2H, m), 2.11 (6H, s), 1.97-1.79 (2H, m).

Example 22

3-(Acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



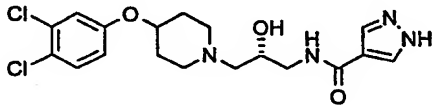
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 480/482 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.88 (1H, s), 7.78 (1H, d), 7.55-7.45 (2H, m), 7.39 (1H, t), 7.31 (1H, d), 6.99 (1H, d), 6.82 (1H, t), 6.75 (1H, dd), 4.37-4.22 (1H, m), 3.99-3.85 (1H, m), 3.77-3.63 (1H, m), 3.38 (1H, quintet), 2.96-2.83 (1H, m), 2.75-2.63 (1H, m), 2.63-2.51 (1H, m), 2.52-2.24 (3H, m), 2.20 (3H, s), 2.08-1.90 (2H, m), 1.90-1.69 (2H, m).

Example 23

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-pyrazole-4-carboxamide



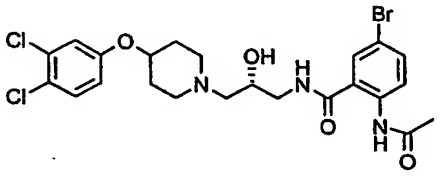
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 413/415 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.02 (2H, s), 7.33 (1H, d), 7.00 (1H, s), 6.95 (1H, t), 6.76 (1H, d), 4.44-4.33 (1H, m), 4.07-3.98 (1H, m), 3.74-3.61 (1H, m), 3.40 (1H, td), 2.98 (1H, td), 2.89-2.77 (2H, m), 2.62 (2H, d), 2.68-2.56 (1H, m), 2.18-1.99 (2H, m), 1.98-1.82 (2H, m).

Example 24

2-(Acetylamino)-5-bromo-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



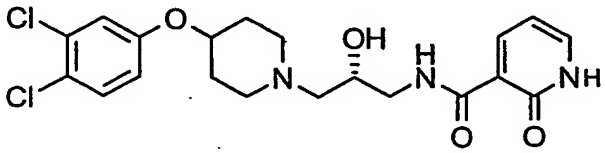
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 558/460/562 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 10.98 (1H, s), 8.52 (1H, d), 7.66 (1H, s), 7.55 (1H, d), 7.32 (1H, d), 7.26 (1H, s), 7.16-7.05 (2H, m), 7.00 (1H, s), 6.76 (1H, d), 4.42-4.30 (1H, m), 4.06-3.94 (1H, m), 3.72-3.59 (2H, m), 3.43-3.29 (1H, m), 2.95 (1H, t), 2.75 (2H, t), 2.59-2.43 (3H, m), 2.19 (3H, s), 2.13-1.96 (5H, m), 1.96-1.78 (3H, m).

Example 25

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-1,2-dihydropyridine-3-carboxamide



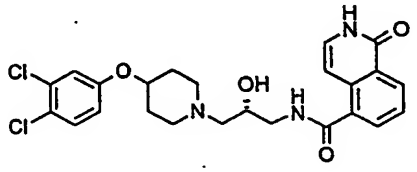
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 440/442 $(M+H)^+$.

^{1}H NMR δ ($CDCl_3$) 9.86 (1H, t), 8.61 (1H, dd), 7.53 (1H, dd), 7.31 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 6.52 (1H, t), 4.33-4.24 (1H, m), 3.97-3.89 (1H, m), 3.70 (1H, ddd), 3.44 (1H, td), 2.94-2.85 (1H, m), 2.73-2.63 (1H, m), 2.59-2.50 (1H, m), 2.49-2.37 (2H, m), 2.30 (1H, t), 2.04-1.90 (2H, m), 1.87-1.72 (2H, m).

Example 26

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-5-carboxamide



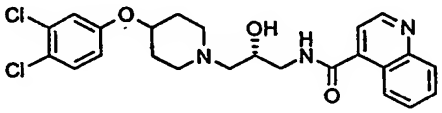
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 490/492 $(M+H)^+$

^{1}H NMR δ (DMSO) 11.34 (1H, d), 8.46 (1H, t), 8.28 (1H, d), 7.78 (1H, dd), 7.50 (1H, t), 7.49 (1H, d), 7.25 (1H, d), 7.23-7.16 (1H, m), 6.98 (1H, dd), 6.81 (1H, d), 4.72 (1H, d), 4.49-4.37 (1H, m), 3.87-3.76 (1H, m), 3.46-3.35 (1H, m), 3.30-3.16 (1H, m), 2.83-2.67 (2H, m), 2.47-2.23 (4H, m), 1.97-1.84 (2H, m), 1.68-1.50 (2H, m).

Example 27

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoline-4-carboxamide



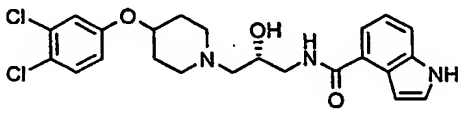
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 474/476 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 1.69-1.79 (m, 2H), 1.90-2.00 (m, 2H), 2.53-2.65 (m, 4H), 2.84-2.94 (m, 2H), 3.39 (dd, 1H), 3.54 (dd, 1H), 3.99-4.05 (m, 1H), 4.33-4.40 (m, 1H), 6.81 (dd, 1H), 7.03 (d, 1H), 7.29 (d, 1H), 7.52 (d, 1H), 7.59 (t, 1H), 7.73 (t, 1H), 8.00 (d, 1H), 8.15 (d, 1H), 8.83 (d, 1H).

Example 28

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-indole-4-carboxamide



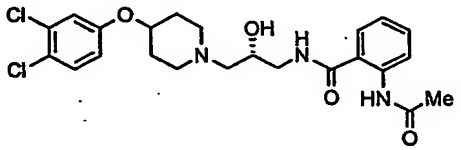
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 462/464 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 1.82-1.91 (m, 2H), 2.00-2.13 (m, 2H), 2.63-2.76 (m, 4H), 2.96-3.05 (m, 2H), 3.44 (dd, 1H), 3.54 (dd, 1H), 4.04-4.11 (m, 1H), 4.43-4.50 (m, 1H), 5.50 (s, 1H), 6.56 (d, 1H), 6.90 (dd, 1H), 7.12 (d, 1H), 7.32 (d, 1H), 7.38 (d, 1H), 7.43 (d, 1H), 7.63 (dd, 1H), 8.14 (s, 1H).

Example 29

2-(Acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



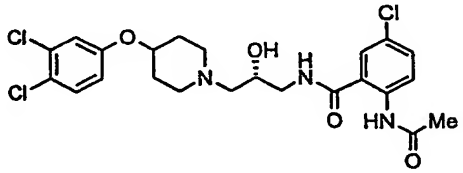
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 480/482 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 11.05 (1H, bd s), 8.60 (1H, d), 7.52-7.46 (2H, m), 7.31 (1H, d), 7.08 (1H, t), 6.99 (1H, d), 6.81 (1H, bd s), 6.76 (1H, dd), 4.36-4.28 (1H, m), 3.96-3.90 (1H, m), 3.72-3.64 (1H, m), 3.40-3.32 (1H, m), 2.94-2.86 (2H, m), 2.72-2.58 (2H, m), 2.49-2.31 (3H, m), 2.20 (3H, s), 2.03-1.93 (2H, m), 1.89-1.79 (2H, m).

Example 30

2-(Acetylamino)-5-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



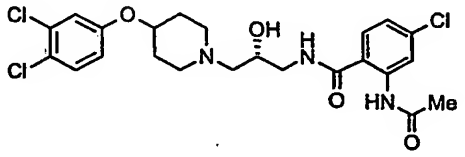
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 514/516/518 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 10.94 (1H, bd s), 8.59 (1H, d), 7.47 (1H, d), 7.43 (1H, dd), 7.32 (1H, d), 7.00 (1H, d), 6.87 (1H, bd s), 6.76 (1H, dd), 4.36-4.28 (1H, m), 3.97-3.90 (1H, m), 3.68-3.61 (1H, m), 3.38-3.32 (1H, m), 2.94-2.88 (1H, m), 2.72-2.58 (2H, m), 2.50-2.33 (3H, m), 2.19 (3H, s), 2.05-1.95 (2H, m), 1.90-1.80 (2H, m).

Example 31

2-(Acetylamino)-4-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



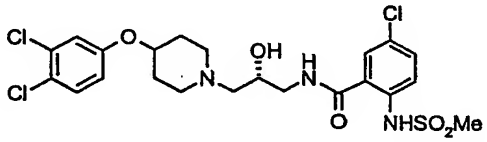
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 514/516/518 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 11.19 (1H, bd s), 8.73 (1H, d), 7.42 (1H, d), 7.32 (1H, d), 7.05 (1H, d), 7.00 (1H, d), 6.78-6.74 (2H, m), 4.36-4.28 (1H, m), 3.96-3.88 (1H, m), 3.70-3.62 (1H, m), 3.38-3.30 (1H, m), 2.94-2.88 (1H, m), 2.70 – 2.58 (2H, m), 2.49-2.30 (3H, m), 2.20 (3H, s), 2.04-1.96 (2H, m), 1.90-1.78 (2H, m).

Example 32

5-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulphonyl)amino]benzamide



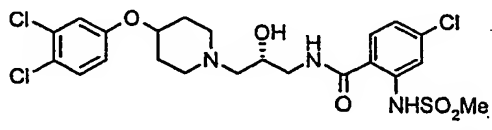
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 550/552/554 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.69 (1H, d), 7.52 (1H, s), 7.45 (1H, d), 7.31 (1H, d), 7.00 (1H, d), 6.75 (1H, dd), 4.36-4.28 (1H, m), 3.96-3.90 (1H, m), 3.72-3.64 (1H, m), 3.36-3.30 (1H, m), 3.04 (3H, s), 2.95-2.89 (1H, m), 2.74-2.56 (2H, m), 2.50-2.30 (3H, m), 2.05-1.95 (2H, m), 1.90-1.88 (2H, m).

Example 33

4-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulphonyl)amino]benzamide



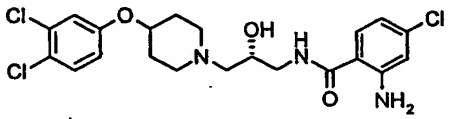
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 550/552/554 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.75 (1H, d), 7.48 (1H, d), 7.31 (1H, d), 7.09 (1H, dd), 7.00 (1H, d), 6.75 (1H, dd), 4.38-4.28 (1H, m), 3.97-3.87 (1H, m), 3.72-3.66 (1H, m), 3.34-3.28 (1H, m), 3.08 (3H, s), 2.98-2.90 (1H, m), 2.76-2.58 (2H, m), 2.50-2.30 (3H, m), 2.10-1.94 (2H, m), 1.90-1.74 (2H, m).

Example 34

2-Amino-4-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



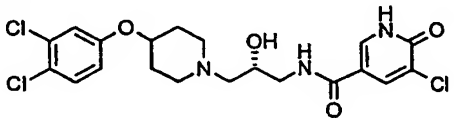
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 472/474/476 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 7.27 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 6.67 (1H, d), 6.61 (1H, dd), 6.55 (1H, t), 5.64 (2H, bd s), 4.34-4.24 (1H, m), 3.92-3.82 (1H, m), 3.68-3.62 (1H, m), 3.36-3.29 (1H, m), 2.94-2.86 (1H, m), 2.70-2.54 (2H, m), 2.47-2.29 (2H, m), 2.26-2.16 (1H, m), 2.04-1.94 (2H, m), 1.88-1.78 (2H, m).

Example 35

5-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-6-oxo-1,6-dihydropyridine-3-carboxamide



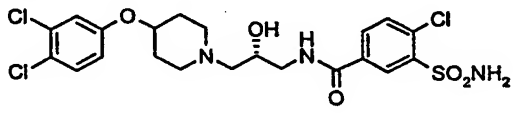
To a solution of (2*R*)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (150 mg, 0.47 mmol) and triethylamine (48 mg, 66 μl, 0.47 mmol) in dichloromethane (20 ml) was added a solution of 5-chloro-6-hydroxynicotinyl chloride (90 mg, 0.47 mmol) in dichloromethane (10 ml). The mixture was stirred at room temperature for 3h and then the solution was concentrated *in vacuo* to leave a crude oil. Purification by reverse phase HPLC (Symmetry, 0.1% ammonium acetate / acetonitrile) afforded the title compound as a colourless glass (150 mg, 67%).

MS (APCI) 474/476/478 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.07 (1H, d), 8.04 (1H, d), 7.31 (1H, d), 7.09 (1H, bd s), 6.99 (1H, d), 6.75 (1H, dd), 4.36-4.26 (1H, m), 4.00-3.90 (1H, m), 3.68-3.58 (1H, m), 3.32-3.22 (1H, m), 2.96-2.86 (1H, m), 2.76-2.58 (2H, m), 2.51-2.35 (3H, m), 2.04-1.94 (2H, m), 1.88-1.76 (2H, m).

Example 36

2-(Aminosulphonyl)-4-chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzamide



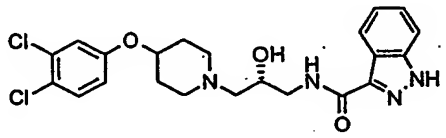
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 536/538/540 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.39 (1H, d), 7.90 (1H, bd s), 7.78 (1H, dd), 7.45 (1H, d), 7.32 (1H, d), 7.00 (1H, d), 6.76 (1H, dd), 4.38-4.22 (2H, m), 3.76-3.62 (1H, m), 3.30-3.20 (1H, m), 3.10-3.00 (1H, m), 2.80-2.68 (2H, m), 2.60-2.40 (3H, m), 2.10-2.00 (2H, m), 1.96-1.86 (2H, m).

Example 37

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*1H*-indazole-3-carboxamide



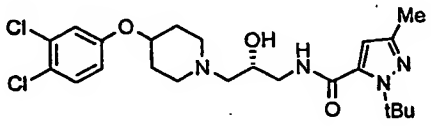
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 463/465 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.43-8.33 (2H, m), 7.54 (1H, d), 7.43 (1H, t), 7.32 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 4.38-4.28 (1H, m), 4.15-4.05 (1H, m), 3.75-3.65 (1H, m), 3.60-3.48 (1H, m), 3.02-2.92 (1H, m), 2.80-2.50 (4H, m), 2.45-2.37 (1H, m), 2.10-1.95 (2H, m), 1.90-1.75 (2H, m).

Example 38

1-*tert*-Butyl-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-methyl-*1H*-pyrazole-5-carboxamide



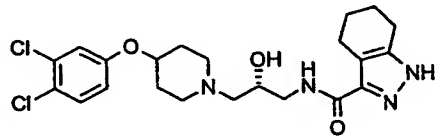
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 483/485 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 6.99 (1H, d), 6.75 (1H, dd), 6.43 (1H, bd s), 6.21 (1H, s), 4.35-4.25 (1H, m), 3.92-3.82 (1H, m), 3.70-3.58 (1H, m), 3.38-3.28 (1H, m), 2.95-2.85 (2H, m), 2.70-2.50 (2H, m), 2.45-2.30 (3H, m), 2.24 (3H, s), 2.05-1.90 (2H, m), 1.90-1.78 (2H, m), 1.67 (9H, s).

Example 39

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4,5,6,7-tetrahydro-*2H*-indazole-3-carboxamide



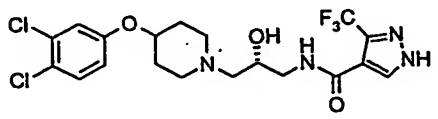
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 467/469 $(M+H)^+$

^{1}H NMR δ (DMSO) 12.69 (1H, s), 7.83 (1H, bd s), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.80 (1H, d), 4.43 (1H, quintet), 3.73 (1H, q), 3.39-3.16 (2H, m), 2.80-2.52 (6H, m), 2.38-2.23 (4H, m), 1.96-1.86 (2H, m), 1.78-1.58 (6H, m).

Example 40

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide



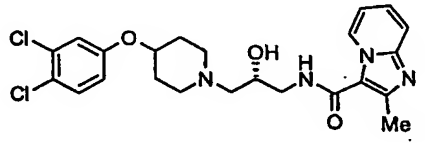
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 481/483 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.11 (1H, s), 7.32 (1H, d), 7.00 (1H, d), 6.75 (1H, dd), 6.70 (1H, bd s), 4.38-4.28 (1H, m), 4.00-3.90 (1H, m), 3.70-3.60 (1H, m), 3.42-3.32 (1H, m), 2.98-2.88 (1H, m), 2.75-2.58 (2H, m), 2.50-2.36 (3H, m), 2.10-1.96 (2H, m), 1.92-1.76 (2H, m).

Example 41

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide



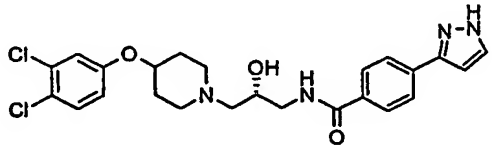
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 477/479 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 9.40 (1H, d), 7.58 (1H, d), 7.36-7.30 (2H, m), 7.00 (1H, d), 6.92 (1H, t), 6.76 (1H, dd), 6.35 (1H, bd s), 4.38-4.28 (1H, m), 4.01-3.93 (1H, m), 3.82-3.72 (1H, m), 3.48-3.40 (1H, m), 2.98-2.90 (1H, m), 2.75 (3H, s), 2.70-2.58 (1H, m), 2.54-2.30 (4H, s), 2.06-1.96 (2H, m), 1.94-1.76 (2H, m).

Example 42

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(*1H*-pyrazol-3-yl)benzamide



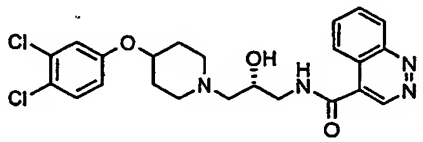
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 489/491 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.84 (2H, d), 7.76 (2H, d), 7.64 (1H, d), 7.34-7.29 (2H, m), 7.00 (1H, d), 6.75 (1H, dd), 6.66 (1H, d), 4.45-4.35 (1H, m), 4.18-4.08 (1H, m), 3.78-3.66 (1H, m), 3.52-3.42 (1H, m), 3.06-2.96 (1H, m), 2.90-2.80 (2H, m), 2.75-2.63 (3H, m), 2.18-2.03 (2H, m), 2.00-1.80 (2H, m).

Example 43

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}cinnoline-4-carboxamide



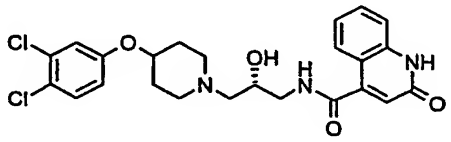
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 475/477 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 9.41 (1H, s), 8.61 (1H, d), 8.38 (1H, d), 7.94-7.82 (2H, m), 7.33 (1H, d), 7.20 (1H, bd s), 7.01 (1H, d), 6.76 (1H, dd), 4.46-4.36 (1H, m), 4.18-4.08 (1H, m), 3.88-3.78 (1H, m), 3.56-3.46 (1H, m), 3.06-2.96 (1H, m), 2.94-2.78 (2H, m), 2.70-2.60 (3H, m), 2.03-1.89 (4H, m).

Example 44

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-1,2-dihydroquinoline-4-carboxamide



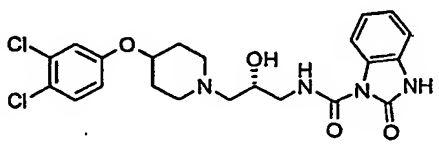
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 490/492 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.69 (1H, t), 7.74 (1H, d), 7.53 (1H, t), 7.49 (1H, d), 7.34 (1H, d), 7.25 (1H, d), 7.18 (1H, t), 6.98 (1H, dd), 6.54 (1H, s), 4.50-4.40 (1H, m), 3.87-3.77 (1H, m), 3.48-3.40 (1H, m), 3.28-3.18 (1H, m), 2.82-2.70 (2H, m), 2.44-2.24 (4H, m), 1.97-1.87 (2H, m), 1.68-1.56 (2H, m).

Example 45

N-{3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide



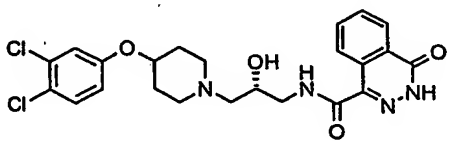
Prepared as described in Example 35, using 2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carbonyl chloride.

MS (APCI) 479/481 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 9.02 (1H, t), 8.17-8.14 (1H, d), 7.32 (1H, d), 7.18-7.12 (2H, m), 7.08-7.05 (1H, m), 7.00 (1H, d), 6.75 (1H, dd), 4.42-4.32 (1H, m), 4.16-4.06 (1H, m), 3.71-3.61 (1H, m), 3.49-3.39 (1H, m), 3.04-2.94 (1H, m), 2.85-2.75 (2H, m), 2.71-2.57 (3H, m), 2.16-1.98 (2H, m), 1.96-1.80 (2H, m).

Example 46

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-oxo-3,4-dihydrophthalazine-1-carboxamide



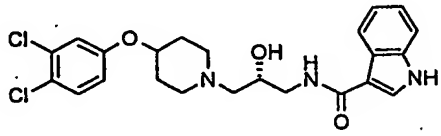
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 491/493/495 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 9.13 (1H, d), 8.43 (1H, d), 7.91-75 (3H, m), 7.32 (1H, d), 7.00 (1H, d), 6.76 (1H, dd), 4.40-4.32 (1H, m), 4.08-3.98 (1H, m), 3.76-3.66 (1H, m), 3.46-3.38 (1H, m), 3.00-2.92 (1H, m), 2.80-2.66 (2H, m), 2.58-2.44 (3H, m), 2.14-1.98 (2H, m), 1.96-1.80 (2H, m).

Example 47

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-indole-3-carboxamide



Prepared as described in Example 1 following Preparation 7.

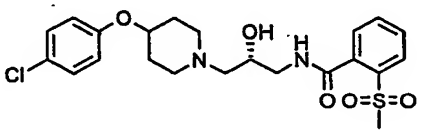
MS (APCI) 462/464/466 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 9.03 (1H, bd s), 8.07-8.04 (1H, d), 7.84 (1H, s), 7.45-7.41 (1H, m), 7.32 (1H, d), 7.28-7.22 (2H, m), 6.99 (1H, d), 6.82 (1H, t), 6.74 (1H, dd), 4.44-4.34

(1H, m), 4.16-4.06 (1H, m), 3.78-3.68 (1H, m), 3.56-3.44 (1H, m), 3.04-2.94 (1H, m), 2.92-2.82 (2H, m), 2.77-2.65 (3H, m), 2.18-1.98 (2H, m), 1.98-1.78 (2H, m).

Example 48

N-{(2*R*)-3-[4-(4-Chlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylsulfonyl)benzamide



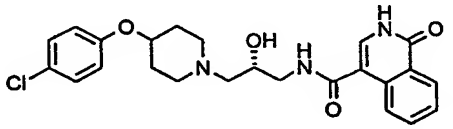
Prepared as described in Example 1 following Preparation 4.

MS (APCI) 467/469 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.08 (1H, d), 7.79 (1H, t), 7.71 (1H, t), 7.61 (1H, d), 7.26 (2H, d), 6.95 (2H, d), 4.56-4.45 (1H, m), 4.21-4.08 (1H, m), 3.47 (2H, d), 3.35 (3H, s), 3.22-3.08 (2H, m), 3.01-2.77 (4H, m), 2.18-2.00 (2H, m), 1.99-1.83 (2H, m).

Example 49

N-{(2*R*)-3-[4-(4-Chlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



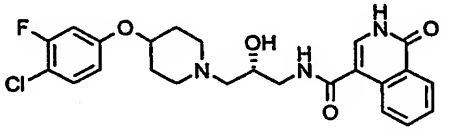
Prepared as described in Example 1 following Preparation 4.

MS (APCI) 466/468 $(M+H)^+$

^{1}H NMR δ (DMSO) 11.57 (1H, d), 8.30 (1H, t), 8.22 (2H, d), 7.73 (1H, t), 7.58-7.45 (2H, m), 7.30 (2H, d), 6.97 (2H, d), 4.75 (1H, s), 4.41-4.29 (1H, m), 3.87-3.74 (1H, m), 3.46-3.26 (1H, m), 3.22-3.07 (1H, m), 2.85-2.67 (2H, m), 2.41-2.21 (4H, m), 2.00-1.84 (2H, m), 1.70-1.51 (2H, m).

Example 50

N-{(2*R*)-3-[4-(4-Chloro-3-fluorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



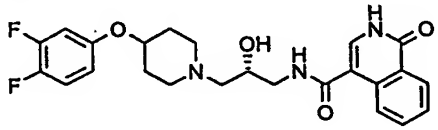
Prepared as described in Example 1 following Preparation 5.

MS (APCI) 474/476 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, d), 8.08 (1H, d), 7.67 (1H, ddd), 7.48 (2H, t), 7.21 (1H, t), 6.75 (1H, d), 6.66 (1H, ddd), 4.30 (1H, dq), 3.95-3.87 (1H, m), 3.45 (1H, dd), 3.29-3.24 (1H, m), 2.80-2.69 (2H, m), 2.45-2.31 (4H, m), 1.95-1.86 (2H, m), 1.73-1.62 (2H, m).

Example 51

N-{(2*R*)-3-[4-(3,4-Difluorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



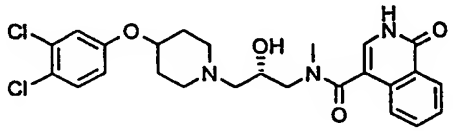
Prepared as described in Example 1 following Preparation 6.

MS (APCI) 458 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, dd), 8.08 (1H, d), 7.67 (1H, ddd), 7.50-7.46 (2H, m), 7.03 (1H, dt), 6.76 (1H, ddd), 6.63-6.59 (1H, m), 4.24 (1H, dquintet), 3.94-3.87 (1H, m), 3.45 (1H, dd), 3.26 (1H, dd), 2.74 (2H, d), 2.45-2.30 (4H, m), 1.90 (2H, dt), 1.72-1.61 (2H, m).

Example 52

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*N*-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



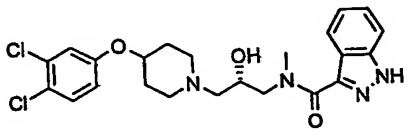
Prepared as described in Example 1 following Preparation 12.

MS (APCI) 504/506 $(M+H)^+$

^{1}H NMR δ (DMSO) 1.25-1.42 (m, 1H), 1.57-1.73 (m, 2H), 1.89-2.15 (m, 3H), 2.26-2.42 (m, 2H), 2.69-2.85 (m, 1H), 2.90-3.15 (m, 4H), 3.63-3.77 (m, 1H), 3.97-4.09 (m, 1H), 4.26-4.49 (m, 1H), 4.79-4.95 (m, 1H), 6.91-7.01 (m, 1H), 7.18-7.31 (m, 2H), 7.45-7.57 (m, 3H), 7.73 (t, 1H), 8.23 (d, 1H), 11.51 (s, 1H).

Example 53

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*N*-methyl-1*H*-indazole-3-carboxamide



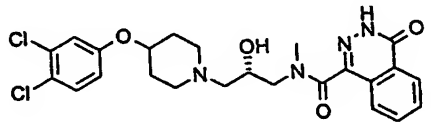
Prepared as described in Example 1 following Preparation 12.

MS (APCI) 477/479 $(M+H)^+$

^{1}H NMR δ (DMSO) 1.36-1.51 (m, 1H), 1.58-1.67 (m, 1H), 1.72-1.81 (m, 1H), 1.86-1.96 (m, 1H), 2.04-2.21 (m, 2H), 2.26-2.39 (m, 2H), 2.71-2.81 (m, 1H), 3.13 (s, 3H), 3.49-3.57 (m, 1H), 3.78-3.93 (m, 1H), 3.98-4.06 (m, 1H), 4.31-4.48 (m, 1H), 4.71-4.83 (m, 1H), 6.93-7.00 (m, 1H), 7.16-7.25 (m, 2H), 7.34-7.43 (m, 1H), 7.49 (d, 1H), 7.58 (t, 1H), 7.95 (dd, 1H), 13.34-13.49 (m, 1H).

Example 54

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-*N*-methyl-4-oxo-3,4-dihydrophthalazine-1-carboxamide



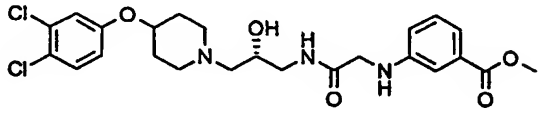
Prepared as described in Example 1 following Preparation 12.

MS (APCI) 505/507 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 1.44-1.55 (m, 1H), 1.69-1.80 (m, 2H), 1.93-2.02 (m, 1H), 2.15-2.24 (m, 1H), 2.19 (d, 1H), 2.46-2.60 (m, 2H), 2.84-2.93 (m, 1H), 3.20 (s, 3H), 3.42-3.51 (m, 1H), 3.75 (dd, 1H), 3.84 (qt, 1H), 4.16-4.25 (m, 1H), 4.35-4.41 (m, 1H), 6.79 (ddd, 1H), 7.00 (dd, 1H), 7.28 (dd, 1H), 7.72-7.89 (m, 3H), 8.31 (t, 1H).

Example 55

Benzoic acid, 3-[[2-[[(2*R*)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]amino]-2-oxoethyl]amino]-, methyl ester



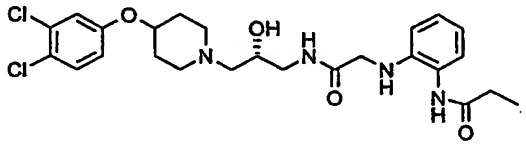
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 510/512 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.17 (1H, t), 7.95 (1H, dd), 7.38 (1H, t), 7.31 (1H, d), 6.98 (1H, d), 6.91 (1H, t), 6.78-6.68 (2H, m), 6.57 (1H, d), 4.32-4.20 (1H, m), 3.92 (2H, d), 3.89 (3H, s), 3.80-3.69 (1H, m), 3.52-3.40 (1H, m), 3.26 (1H, dt), 2.87-2.74 (1H, m), 2.62-2.39 (2H, m), 2.32 (1H, dd), 2.28-2.14 (2H, m), 2.00-1.84 (2H, m), 1.83-1.66 (2H, m).

Example 56

Propanamide, *N*-[2-[[2-[[(2*R*)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]amino]-2-oxoethyl]amino]phenyl]-



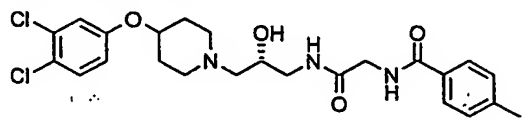
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 523/525 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.48 (1H, t), 7.31 (1H, d), 7.23-7.11 (2H, m), 7.05 (1H, d), 6.98 (2H, d), 6.83-6.71 (2H, m), 6.67 (1H, d), 4.54 (1H, t), 4.31-4.17 (1H, m), 3.92 (1H, d), 3.79-3.66 (1H, m), 3.45 (1H, td), 3.22 (1H, td), 2.78-2.66 (1H, m), 2.61-2.43 (1H, m), 2.49 (2H, q), 2.37 (1H, t), 2.26-2.06 (3H, m), 1.98-1.82 (2H, m), 1.82-1.64 (2H, m), 1.29 (3H, t).

Example 57

Propanamide, *N*-[2-[[2-[[(2*R*)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]amino]-2-oxoethyl]amino]phenyl]-



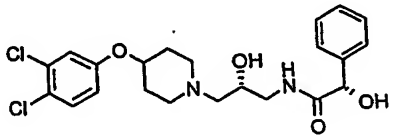
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 494/496 $(M+H)^+$

^1H NMR δ ($CDCl_3$) 7.73 (2H, dd), 7.32 (1H, dd), 7.29-7.21 (2H, m), 7.02-6.97 (1H, m), 6.97-6.88 (1H, m), 6.80-6.71 (1H, m), 6.60-6.49 (1H, m), 4.36-4.23 (1H, m), 4.14 (2H, t), 3.89-3.75 (1H, m), 3.62-3.48 (1H, m), 3.31-3.17 (1H, m), 2.94-2.81 (1H, m), 2.72-2.59 (1H, m), 2.60-2.47 (1H, m), 2.43-2.22 (3H, m), 2.40 (3H, s), 2.05-1.89 (2H, m), 1.88-1.72 (2H, m).

Example 58

(2*S*)-*N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-hyroxy-2-phenylethanamide



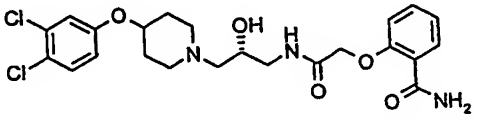
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 453/455/457 $(M+H)^+$

^1H NMR δ ($CDCl_3$) 7.44-7.26 (6H, m), 6.98 (1H, d), 6.74 (1H, dd), 6.54 (1H, bd s), 5.06 (1H, s), 4.34-4.24 (1H, m), 3.83-3.73 (1H, m), 3.56-3.43 (1H, m), 3.32-3.20 (1H, m), 2.88-2.80 (1H, m), 2.62-2.52 (2H, m), 2.33-2.10 (3H, m), 2.02-1.90 (2H, m), 1.86-1.70 (2H, m).

Example 59

2-[2-({(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)-2-oxoethoxy]benzamide



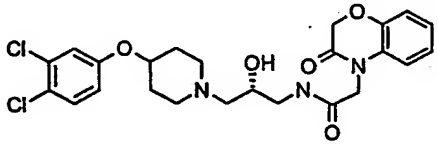
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 496/498 $(M+H)^+$

^1H NMR δ ($CDCl_3$) 7.97 (1H, d), 7.48 (1H, t), 7.36-7.28 (2H, m), 7.17-7.07 (1H, m), 7.13 (2H, t), 6.99 (1H, s), 6.93 (1H, d), 6.75 (1H, d), 5.99 (1H, s), 4.68 (2H, s), 4.35-4.22 (1H, m), 3.89-3.77 (1H, m), 3.67-3.54 (1H, m), 3.22 (1H, quintet), 2.91-2.79 (1H, m), 2.68-2.46 (2H, m), 2.43-2.20 (3H, m), 2.04-1.88 (2H, m), 1.88-1.71 (2H, m).

Example 60

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(3-oxo-2,3-dihydro-*4H*-1,4-benzoxazin-4-yl)acetamide



Prepared as described in Example 1 following Preparation 7.

MS (APCI) 508/510 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.31 (1H, d), 7.08-7.01 (4H, m), 6.99 (1H, d), 6.74 (1H, dd), 6.53 (1H, bd s), 4.69 (2H, s), 4.56 (2H, q), 4.34-4.24 (1H, m), 3.80-3.72 (1H, m), 3.52-3.42 (1H, m), 3.28-3.18 (1H, m), 2.88-2.80 (1H, m), 2.63-2.45 (4H, m), 2.36-2.21 (3H, m), 2.00-1.90 (2H, m), 1.86-1.70 (2H, m).

Further Examples of compounds of the invention which have been prepared as described in Example 1 following Preparation 7 are presented in the Table below.

Example	Name	$(M+H)^+$
61	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methoxybenzamide	452
62	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(methylamino)benzamide	451
63	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}nicotinamide	423
64	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}isonicotinamide	423
65	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(dimethylamino)benzamide	465
66	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide	505
67	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-hydroxynicotinamide	439

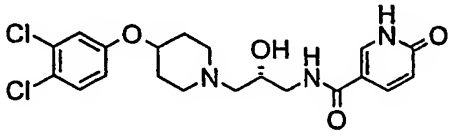
68	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(1H-indol-3-yl)acetamide	475
69	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide	448
70	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4,7-dimethylpyrazolo[5,1-c][1,2,4]triazine-3-carboxamide	492
71	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}pyrazine-2-carboxamide	424
72	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-9H-purine-6-carboxamide	464
73	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoline-6-carboxamide	473
74	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,7-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxamide	491
75	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(pyrimidin-2-ylthio)acetamide	470
76	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-fluoro-1H-indole-2-carboxamide	479
77	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,3-benzothiazole-6-carboxamide	479
78	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-phenyl-1,3-oxazole-4-carboxamide	489
79	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-hydroxypyridine-2-carboxamide	439
80	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide	493
81	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-hydroxypyridine-2-carboxamide	439
82	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-benzimidazole-5-carboxamide	462
83	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-indole-5-carboxamide	461
84	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-	475

	1-methyl-1H-indole-2-carboxamide	
85	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-imidazole-4-carboxamide	412
86	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-indole-6-carboxamide	461
87	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-methyl-1H-indole-3-carboxamide	475
88	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1H-indole-7-carboxamide	461
89	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-[(methylamino)sulfonyl]benzamide	515
90	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3,4-bis(methylsulfonyl)benzamide	578
91	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-pyridin-3-ylacetamide	437
92	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-hydroxy-1H-indole-2-carboxamide	477
93	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,5-dimethyl-1H-pyrazole-3-carboxamide	440
94	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(methylsulfonyl)-1H-indole-2-carboxamide	539
95	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoxaline-6-carboxamide	474
96	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,8-naphthyridine-2-carboxamide	474
97	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}imidazo[2,1-b][1,3]benzothiazole-2-carboxamide	518
98	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,6-dimethylimidazo[1,2-a]pyridine-3-carboxamide	490
99	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-oxo-2,3-dihydro-1H-indazole-4-carboxamide	478
100	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-oxo-2,3-dihydro-1H-indazole-6-carboxamide	478

101	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide	480
102	2-(1H-benzimidazol-1-yl)-N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}acetamide	476
103	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-ethyl-3-methyl-1H-pyrazole-5-carboxamide	454
104	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-methyl-1H-pyrazole-3-carboxamide	426
105	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-methyl-1,2,5-oxadiazole-3-carboxamide	428
106	6-chloro-N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}imidazo[1,2-a]pyridine-2-carboxamide	496
107	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methylimidazo[1,2-a]pyridine-3-carboxamide	476
108	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}imidazo[1,2-a]pyrimidine-2-carboxamide	463
109	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(4-methylpyrimidin-2-yl)thio]acetamide	484
110	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-oxo-1,4-dihydroquinoline-2-carboxamide	489
111	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}quinoline-8-carboxamide	473
112	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-methylimidazo[1,2-a]pyridine-2-carboxamide	476
113	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}imidazo[1,2-a]pyridine-2-carboxamide	462
114	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,6-naphthyridine-2-carboxamide	474
115	N-{(2R)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,1,3-benzoxadiazole-5-carboxamide 1-oxide	480

Example 116

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-1,6-dihydropyridine-3-carboxamide



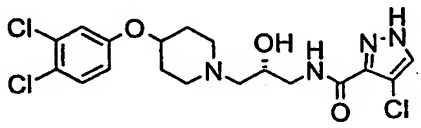
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 440/442 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.07 (1H, d), 7.99 (1H, dd), 7.39 (1H, d), 7.15 (1H, d), 6.92 (1H, dd), 6.53 (1H, d), 4.52 (1H, septet), 4.09-4.01 (1H, m), 3.49 (1H, dd), 3.34 (1H, d), 3.11-3.02 (2H, m), 2.86-2.67 (4H, m), 2.14-2.03 (2H, m), 1.95 (3H, s), 1.97-1.84 (2H, m).

Example 117

4-Chloro-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1*H*-pyrazole-3-carboxamide



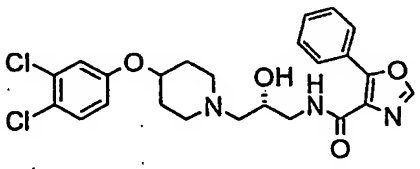
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 447/449 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.77 (1H, s), 7.37 (1H, d), 7.09 (1H, d), 6.88 (1H, dd), 4.39 (1H, t), 3.95 (1H, quintet), 3.49 (1H, dd), 3.40 (1H, dd), 2.86-2.77 (2H, m), 2.52-2.39 (2H, m), 2.49 (2H, d), 2.06-1.96 (2H, m), 1.85-1.74 (2H, m).

Example 118

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-phenyl-1,3-oxazole-4-carboxamide



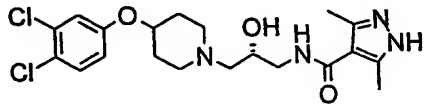
Prepared as described in Example 35 following Preparation 7 from 5-phenyl-1,3-oxazole-4-carbonyl chloride.

MS (APCI) 490/492 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.12 (1H, s), 8.10-8.08 (2H, m), 7.40-7.35 (3H, m), 7.29 (1H, d), 7.04 (1H, d), 6.81 (1H, dd), 4.39 (1H, septet), 3.95 (1H, quintet), 3.44-3.33 (2H, m), 2.96-2.87 (2H, m), 2.67-2.55 (4H, m), 2.03-1.93 (2H, m), 1.85 (3H, s), 1.85-1.75 (2H, m).

Example 119

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3,5-dimethyl-1*H*-pyrazole-4-carboxamide



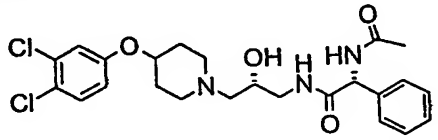
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 441/443 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.28 (1H, d), 7.00 (1H, d), 6.79 (1H, dd), 4.34-4.26 (1H, m), 3.86 (1H, quintet), 3.41 (1H, dd), 3.21 (1H, dd), 2.78-2.67 (2H, m), 2.41-2.30 (4H, m), 2.29 (6H, s), 1.95-1.86 (2H, m), 1.73-1.63 (2H, m).

Example 120

(2*R*)-2-(Acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-phenylethanamide



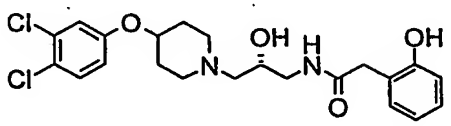
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 494/496 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.34 (2H, d), 7.29-7.18 (4H, m), 6.99 (1H, t), 6.78 (1H, dd), 5.29 (1H, s), 4.27 (1H, septet), 3.76-3.65 (1H, m), 3.26-3.08 (2H, m), 2.65-2.49 (2H, m), 2.30-2.15 (4H, m), 1.91 (3H, s), 1.90-1.81 (2H, m), 1.69-1.58 (2H, m).

Example 121

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(2-hydroxyphenyl)acetamide



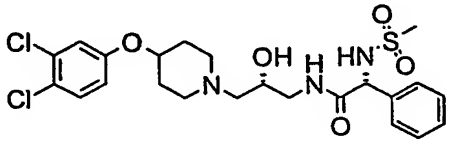
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 453/455 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.28 (1H, d), 7.05-6.97 (3H, m), 6.78 (1H, dd), 6.72-6.67 (2H, m), 4.27 (1H, dq), 3.72 (1H, quintet), 3.43 (2H, dd), 3.21-3.08 (2H, m), 2.68-2.57 (2H, m), 2.32-2.20 (4H, m), 1.90-1.81 (2H, m), 1.69-1.58 (2H, m).

Example 122

(2*R*)-*N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulfonyl)amino]-2-phenylethanamide



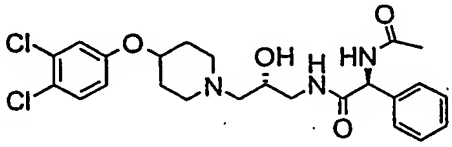
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 530/532 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.37 (2H, d), 7.31-7.21 (4H, m), 6.99 (1H, d), 6.78 (1H, dd), 4.96 (1H, s), 4.27 (1H, septet), 3.70 (1H, quintet), 3.24 (1H, dd), 3.13 (1H, dd), 2.72 (3H, s), 2.66-2.56 (2H, m), 2.32-2.18 (4H, m), 1.91-1.82 (2H, m), 1.70-1.59 (2H, m).

Example 123

(2*S*)-2-(Acetylamino)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-phenylethanamide



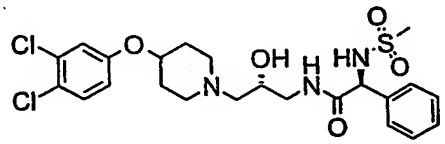
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 494/496 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.34 (2H, d), 7.30-7.18 (4H, m), 6.99 (1H, dd), 6.78 (1H, ddd), 5.29 (1H, s), 4.30-4.23 (1H, m), 3.76-3.65 (1H, m), 3.17-3.07 (2H, m), 2.65-2.48 (2H, m), 2.30-2.14 (4H, m), 1.92-1.80 (2H, m), 1.91 (3H, s), 1.68-1.57 (2H, m).

Example 124

(2*S*)-*N*-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-[(methylsulfonyl)amino]-2-phenylethanamide



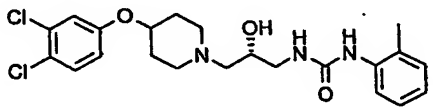
Prepared as described in Example 1 following Preparation 7.

MS (APCI) 530/5322 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 7.47 (2H, d), 7.40-7.30 (4H, m), 7.08 (1H, d), 6.87 (1H, dd), 5.06 (1H, s), 4.39-4.32 (1H, m), 3.83 (1H, quintet), 3.27 (2H, d), 2.80 (3H, s), 2.73-2.59 (2H, m), 2.38-2.24 (2H, m), 2.28 (2H, d), 1.99-1.89 (2H, m), 1.78-1.67 (2H, m).

Example 125

1-{(R)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-o-tolyl-urea



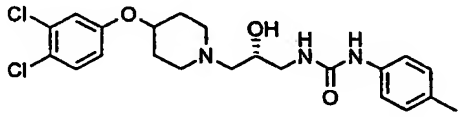
A solution of o-tolylisocyanate (64ml, 0.51mmol) in dichloromethane (1ml) was added to a suspension of (2R)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0,15g, 0.47mmol) in dichloromethane (3ml) over a five minute period. After 1h methanol (1ml) was added and the solvents removed under vacuum. The residue was purified by reverse phase chromatography (C8 Symmetry column) to give the title compound (87mg).

MS (APCI) 452/454 $(M+H)^+$

^{1}H NMR δ (DMSO) 7.81 (1H, d), 7.78 (1H, s), 7.50 (1H, dd), 7.26 (1H, dd), 7.10 (1H, t), 7.05 (1H, s), 6.99 (1H, ddd), 6.86 (1H, t), 6.63 (1H, t), 4.74 (1H, d), 4.49-4.40 (1H, m), 3.72-3.63 (1H, m), 3.32-3.30 (1H, m), 2.99-2.90 (1H, m), 2.79-2.67 (2H, m), 2.35-2.24 (4H, m), 2.18 (3H, s), 1.97-1.88 (2H, m), 1.69-1.56 (2H, m).

Example 126

1-{(R)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-p-tolyl-urea



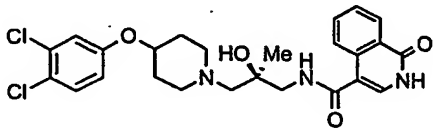
Prepared as described in Example 125 following Preparation 1.

MS (APCI) 452/454 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.52 (1H, s), 7.55 (1H, d), 7.31 (2H, d), 7.31 (1H, s), 7.07 (2H, d), 7.03 (1H, d), 6.15 (1H, t), 4.82-4.76 (1H, m), 4.55-4.45 (1H, m), 3.76-3.67 (1H, m), 3.36-3.32 (1H, m), 3.03-2.95 (1H, m), 2.83-2.72 (2H, m), 2.40-2.31 (4H, m), 2.27 (3H, s), 2.03-1.92 (2H, m), 1.75-1.61 (2H, m).

Example 127

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



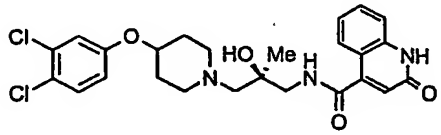
Prepared as described in Example 1 following Preparation 9.

MS (APCI) 504/506/508 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.37 (1H, d), 8.18 (1H, d), 7.78 (1H, t), 7.59 (1H, s), 7.58 (1H, t), 7.37 (1H, d), 7.07 (1H, d), 6.86 (1H, dd), 4.33-4.28 (1H, m), 3.60-3.45 (2H, m), 3.04-2.92 (2H, m), 2.60-2.45 (4H, m), 1.98-1.86 (2H, m), 1.72-1.60 (2H, m), 1.25 (3H, s).

Example 128

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-2-oxo-1,2-dihydroquinoline-4-carboxamide



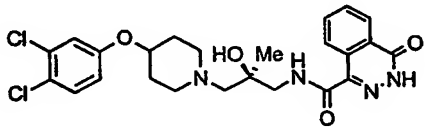
Prepared as described in Example 1 following Preparation 9.

MS (APCI) 504/506/508 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.93 (1H, d), 7.53 (1H, t), 7.34-7.20 (4H, m), 6.98 (1H, d), 6.75-6.69 (2H, m), 4.32-4.22 (1H, m), 3.68-3.40 (2H, m), 3.00-2.80 (2H, m), 2.70-2.48 (4H, m), 2.00-1.86 (2H, m), 1.84-1.72 (2H, m), 1.26 (3H, s).

Example 129

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-4-oxo-3,4-dihydrophthalazine-1-carboxamide



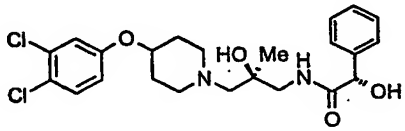
Prepared as described in Example 1 following Preparation 9.

MS (APCI) 505/507/509 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 10.18 (1H, bs), 9.15 (1H, d), 8.44 (1H, d), 8.06 (1H, bd s), 7.89 (1H, t), 7.81 (1H, t), 7.31 (1H, d), 7.01 (1H, d), 6.78 (1H, dd), 4.35-4.25 (1H, m), 3.58-3.37 (2H, m), 3.04-2.82 (2H, m), 2.66-2.46 (4H, m), 2.06-1.96 (2H, m), 1.94-1.80 (2H, m), 1.23 (3H, s).

Example 130

(2*S*)-*N*-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-2-hydroxy-2-phenethanamide



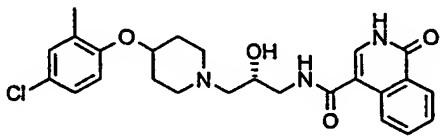
Prepared as described in Example 1 following Preparation 9.

MS (APCI) 467/469/471 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 7.46-7.29 (6H, m), 6.98 (1H, d), 6.78 (1H, bd s), 6.75 (1H, dd), 5.08 (1H, s), 4.28-4.20 (1H, m), 3.71 (1H, bd s), 3.35-3.20 (2H, m), 2.86-2.69 (2H, m), 2.53-2.39 (2H, m), 2.31 (2H, s), 1.97-1.85 (2H, m), 1.82-1.70 (2H, m), 1.04 (3H, s).

Example 131

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



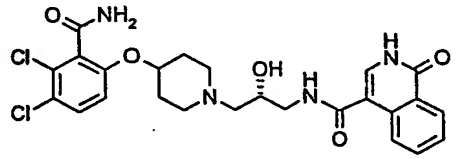
Prepared as described in Example 1 following Preparation 10.

MS (APCI) 470/472 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, d), 8.08 (1H, d), 7.67 (1H, t), 7.48 (2H, t), 7.05-6.96 (2H, m), 6.77 (1H, d), 4.36-4.25 (1H, m), 3.98-3.87 (1H, m), 3.45 (1H, dd), 3.28 (1H, dd), 2.80-2.67 (2H, m), 2.49-2.34 (4H, m), 2.08 (3H, s), 1.98-1.84 (2H, m), 1.78-1.64 (2H, m).

Example 132

N-((2*R*)-3-{4-[2-(Aminocarbonyl)-3,4-dichlorophenoxy]piperidin-1-yl}-2-hydroxypropyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



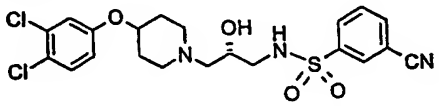
The crude amine product obtained from Preparation 11 was redissolved in dichloromethane and treated with diisopropylethylamine (0.85ml) and 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride (0.40g) at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate solution and the mixture concentrated *in vacuo*, azeotoping with toluene. Extraction of the solid residue into dichloromethane/methanol, filtering solids and chromatography on silica (dichloromethane:7N ammonia in methanol/15:2) gave the target compound as a white solid (0.31g).

MS (APCI) 533/535 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, d), 8.12 (1H, d), 7.69 (1H, m), 7.55 (1H, s), 7.49 (1H, m), 7.44 (1H, d), 7.05 (1H, d), 4.20 (1H, m), 3.55-2.96 (10H, m), 2.25-1.98 (4H, m).

Example 133

3-Cyano-*N*-{(2*S*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide



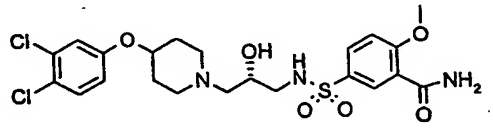
To a solution of (2*R*)-1-amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.200g, 0.63mmol) in 4ml of pyridine at 0°C was added 3-cyanobenzenesulfonyl chloride (0.127g, 0.63mmol). After 30 min, the reaction was allowed to warm to room temperature and was stirred for 2h. The reaction was concentrated under vacuum, and the residue partitioned between 10% aqueous sodium hydrogen carbonate and ethyl acetate. The organic layer was washed with water, then brine and dried over magnesium sulfate. The crude material was purified on silica gel (0 to 5% 7N ammonia in methanol/dichloromethane) to afford the title compound as a white foam (0.120g).

MS (ESI) 484/486 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.22 (1H, d), 8.16-8.07 (2H, d), 7.82 (2H, t), 7.50 (1H, d), 7.25 (1H, d), 6.97 (1H, dd), 4.71 (d, 1H), 4.47-4.34 (1H, m), 3.63-3.51 (1H, m), 2.93 (1H, dd), 2.71 (1H, dd), 2.69-2.55 (2H, m), 2.32-2.12 (4H, m), 1.95-1.79 (2H, m), 1.65-1.45 (2H, m), 1.65-1.45 (2H, m).

Example 134

5-[({(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)-sulfonyl]-2-methoxybenzamide



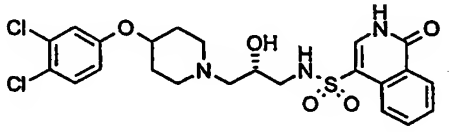
Prepared as described in Example 133 following Preparation 7 using 3-(aminocarbonyl)-4-methoxybenzenesulfonyl chloride.

MS (APCI) 531/533 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.20 (1H, d), 7.87 (1H, dd), 7.73 (2H, s), 7.55 (1H, s), 7.49 (1H, d), 7.32 (1H, d), 7.25 (1H, d), 6.97 (1H, dd), 4.67 (1H, d), 4.41 (1H, septet), 3.96 (3H, s), 3.58 (1H, q), 2.82 (1H, d), 2.68-2.57 (3H, m), 2.30-2.16 (4H, m), 1.91-1.82 (2H, m), 1.60-1.49 (2H, m).

Example 135

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-sulfonamide acetate salt



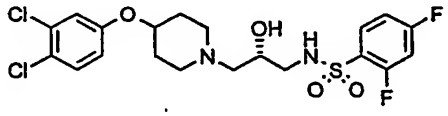
(2R)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.15g) in pyridine (2ml) was treated with 1-oxo-1,2-dihydroisoquinoline-4-sulfonyl chloride (0.11g) and the mixture was stirred at ambient temperature for 18h. After further additions of the sulfonyl chloride (0.05g) and stirring for 24h the solvent was evaporated. Purification by column chromatography and reverse phase HPLC (symmetry C8 column and acetonitrile/0.1% aqueous ammonium acetate) yielded the title compound as a white solid (0.06g).

MS (APCI) 526/528 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.39 (1H, d), 8.32 (1H, d), 7.95 (1H, s), 7.86 (1H, ddd), 7.64 (1H, t), 7.39 (1H, d), 7.11 (1H, d), 6.89 (1H, dd), 4.45-4.39 (1H, m), 3.82-3.75 (1H, m), 3.34 (1H, s), 2.97 (1H, dd), 2.92 (1H, dd), 2.81-2.72 (2H, m), 2.55-2.42 (2H, m), 2.02-1.92 (2H, m), 1.95 (3H, s, OAc), 1.82-1.72 (2H, m).

Example 136

N-{(2*S*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,4-difluorobenzenesulfonamide



Prepared as described in Example 133 following Preparation 7 using 2,4-difluorobenzenesulfonyl chloride.

MS (APCI) 493/495 $(M+H)^+$

^{1}H NMR δ (DMSO) 7.94 (1H, s), 7.86 (1H, td), 7.55 (1H, ddd), 7.49 (1H, d), 7.28 (1H, ddd), 7.25 (1H, d), 6.97 (1H, dd), 4.69 (1H, d), 4.42 (1H, septet), 3.60 (1H, sextet), 2.96 (1H, dd), 2.81 (1H, dd), 2.68-2.58 (2H, m), 2.34-2.16 (4H, m), 1.91-1.82 (2H, m), 1.60-1.49 (2H, m).

Further Examples of compounds of the invention which have been prepared according to Example 133 following Preparation 7 are now listed in the following table.

Example	Name	$(M+H)^+$
137	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}methanesulfonamide	396
138	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide	458
139	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-phenylmethanesulfonamide	472
140	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-methoxybenzenesulfonamide	488
141	N-({5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-2-thienyl}methyl)benzamide	597
142	4-cyano-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide	483
143	N-{5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-4-methyl-1,3-thiazol-2-yl}acetamide	536
144	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}thiophene-2-sulfonamide	464
145	4-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]benzoic acid	502
146	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,5-dimethoxybenzenesulfonamide	518
147	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(phenylsulfonyl)thiophene-2-sulfonamide	604
148	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(1,3-oxazol-5-yl)thiophene-2-sulfonamide	531
149	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]thiophene-2-sulfonamide	612

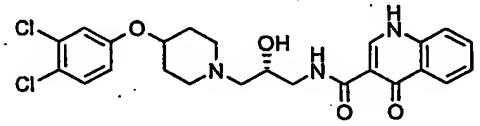
150	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(pyridin-2-yl)thiophene-2-sulfonamide	541
151	5-chloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,3-dimethyl-1H-pyrazole-4-sulfonamide	510
152	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3,5-dimethylisoxazole-4-sulfonamide	477
153	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,1,3-benzothiadiazole-4-sulfonamide	516
154	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-methyl-1H-imidazole-4-sulfonamide	462
155	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,1,3-benzoxadiazole-4-sulfonamide	500
156	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-(isoxazol-3-yl)thiophene-2-sulfonamide	531
157	methyl 3-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]thiophene-2-carboxylate	522
158	2,6-dichloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide	526
159	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-methylbenzenesulfonamide	472
160	3-chloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide	492
161	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}propane-2-sulfonamide	424
162	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}propane-1-sulfonamide	424
163	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-5-methyl-1-phenyl-1H-pyrazole-4-sulfonamide	538
164	3-chloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methylbenzenesulfonamide	506
165	methyl 5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-2-methyl-3-furoate	520

166	methyl 5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-1-methyl-1H-pyrrole-2-carboxylate	519
167	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3,4-dimethoxybenzenesulfonamide	518
168	5-chloro-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}thiophene-2-sulfonamide	498
169	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(morpholin-4-yl)pyridine-3-sulfonamide	544
170	N-{2-chloro-4-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]phenyl}acetamide	549
171	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,3-dihydroxyquinoxaline-6-sulfonamide	542
172	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,4-dimethoxybenzenesulfonamide	518
173	5-[({(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}amino)sulfonyl]-2-methoxybenzamide	531
174	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-methylbenzenesulfonamide	472
175	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2,4-dimethyl-1,3-thiazole-5-sulfonamide	493
176	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-hydroxyquinoxaline-6-sulfonamide	526
177	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonamide	529
178	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}pyridine-3-sulfonamide	459
179	4'-cyano-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}biphenyl-2-sulfonamide	559
180	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,2-dimethyl-1H-imidazole-4-sulfonamide	476

181	4-acetyl-N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide	500
182	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-(methylsulfonyl)benzenesulfonamide	536
183	2-chloro-4-cyano-N-{(2S)-3-[4-(3,4-dichlorophenoxy)-piperidin-1-yl]-2-hydroxypropyl}benzenesulfonamide	517
184	N-{(2S)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1,3,5-trimethyl-1H-pyrazole-4-sulfonamide	490

Example 185

N-[(2*R*)-3-[4-(3,4-Dichlorophenoxy)-1-piperidinyl]-2-hydroxypropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxamide



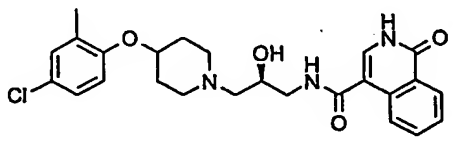
Prepared as described in Example 1 following Preparation 7 using 4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

MS (APCI) 490/492 $(M+H)^+$

^{1}H NMR δ (DMSO) 10.21 (5H, t), 8.74 (6H, s), 8.26 (6H, dd), 7.74 (10H, ddd), 7.68 (8H, d), 7.49 (11H, d), 7.48-7.44 (11H, m), 7.25 (6H, d), 6.98 (6H, dd), 4.80 (4H, s), 4.44 (6H, septet), 3.75 (6H, s), 3.55 (7H, ddd), 3.26-3.19 (20H, m), 2.78-2.68 (12H, m), 2.34 (20H, d), 2.33-2.25 (24H, m), 1.96-1.88 (12H, m), 1.69-1.58 (12H, m).

Example 186

N-{(2*S*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



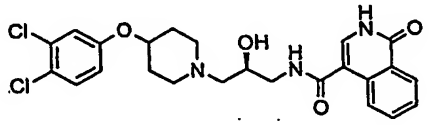
Prepared as described in Example 35 following Preparation 10 using (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate and 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 470/472 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.32 (1H, t), 8.22 (2H, d), 7.73 (1H, td), 7.52 (1H, td), 7.52 (1H, s), 7.20 (1H, d), 7.14 (1H, dd), 6.98 (1H, d), 4.38 (1H, septet), 3.81 (1H, quintet), 3.43-3.36 (1H, m), 3.18-3.11 (1H, m), 2.75-2.63 (2H, m), 2.42-2.28 (4H, m), 2.14 (3H, s), 1.94-1.84 (2H, m), 1.88 (3H, s, OAc), 1.70-1.58 (2H, m).

Example 187

N-{(2*S*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



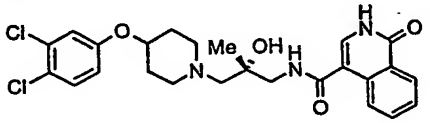
Prepared as described in Example 35 following Preparation 14 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 490/492/494 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.40 (1H, d), 8.21 (1H, d), 7.74 (1H, t), 7.54 (1H, t), 7.50 (1H, s), 7.32 (1H, d), 7.00 (1H, d), 6.76 (1H, dd), 4.36-4.24 (1H, m), 3.99-3.93 (1H, d), 3.73-3.68 (1H, d), 3.33-3.28 (1H, m), 2.96-2.84 (1H, m), 2.75-2.30 (5H, m), 2.04-1.94 (2H, m), 1.88-1.76 (2H, s).

Example 188

N-{(2*S*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



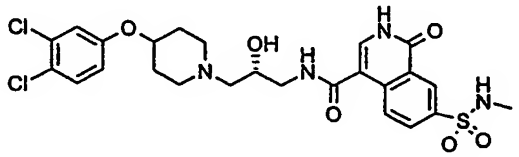
Prepared as described in Example 35 following Preparation 15 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 504/506/508 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.38 (1H,d), 8.19 (1H, d)7.80 (1H, t), 7.61 (1H, t), 7.60 (1H, t), 7.38 (1H, d), 7.09 (1H, d), 6.87 (1H, dd), 4.37-4.30 (1H, m), 3.64 (1H, d), 3.42 (1H, d), 3.03-2.83 (2H, m), 2.60-2.46 (4H, m), 1.96-1.86 (2H, m), 1.72-1.60(2H, m), 1.26 (3H, s).

Example 189

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-[(methylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



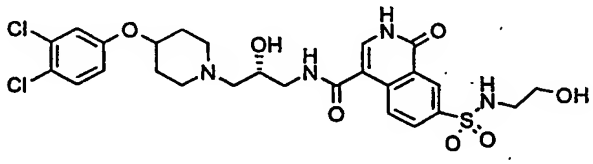
7-[(Methylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (0.1g) in dimethyl formamide (7ml) was treated with N,N-carbonyldiimidazole (0.06g) and the mixture was heated at 55°C for 45 min. (2R)-1-Amino-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propan-2-ol (0.11g) in dimethyl formamide (1ml) was added and the mixture was stirred at ambient temperature for 18h. 1 Drop of water was added and the solvent was evaporated. Purification using reverse phase HPLC (Symmetry C8 column) and acetonitrile/aqueous ammonium acetate as eluent yielded the title compound as a white solid (0.03g).

MS (APCI) 583/585 $(M+H)^+$.

^{1}H NMR δ (DMSO) 8.59 (1H, s), 8.44 (1H, d), 8.42 (1H, t), 8.04 (1H, dd), 7.73 (1H, s), 7.62 (1H, s), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.79 (1H, s), 4.44 (1H, septet), 3.80 (1H, quintet), 3.45-3.37 (1H, m), 3.18-3.11 (1H, m), 2.81-2.69 (2H, m), 2.42 (3H, s), 2.39-2.25 (4H, m), 1.96-1.87 (2H, m), 1.66-1.55 (2H, m).

Example 190

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-{[(2-hydroxyethyl)amino]sulfonyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



Prepared as described in Example 189 following Preparation 7 using 1,2-dihydro-7-[[(2-hydroxyethyl)amino]sulfonyl]-1-oxo-4-isoquinolinecarboxylic acid.

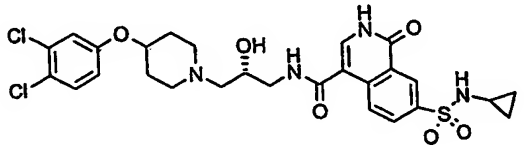
MS (APCI) 613/615 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.61 (1H, s), 8.42 (1H, d), 8.42 (1H, t), 8.07 (1H, dd), 7.71 (1H, s), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.44 (1H, septet), 3.81 (1H, quintet),

3.46-3.37 (1H, m), 3.35 (2H, t), 3.18-3.10 (1H, m), 2.80-2.68 (2H, m), 2.80 (2H, t), 2.42-2.25 (4H, m), 1.96-1.87 (2H, m), 1.88 (3H, s, OAc), 1.66-1.55 (2H, m).

Example 191

7-[(Cyclopropylamino)sulfonyl]-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



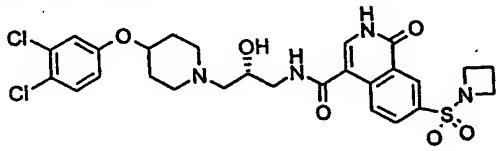
Prepared as described in Example 189 following Preparation 7 using 7-[(cyclopropylamino)sulfonyl]-1,2-dihydro-1-oxo-4-isoquinolinecarboxylic acid.

MS (APCI) 609/611 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.64 (1H, s), 8.44 (1H, d), 8.41 (1H, t), 8.07 (1H, dd), 7.72 (1H, s), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.78 (1H, s), 4.44 (1H, septet), 3.81 (1H, quintet), 3.45-3.38 (1H, m), 3.18-3.10 (1H, m), 2.81-2.69 (2H, m), 2.42-2.25 (4H, m), 2.15-2.09 (1H, m), 1.96-1.86 (2H, m), 1.66-1.54 (2H, m), 0.50-0.44 (2H, m), 0.38-0.32 (2H, m).

Example 192

7-(Azetidin-1-ylsulfonyl)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



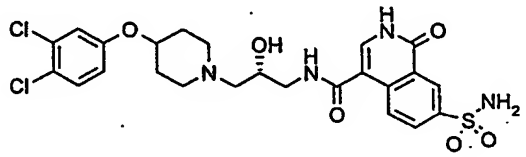
Prepared as described in Example 189 following Preparation 7 using 7-(azetidin-1-ylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 609/611 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.53 (1H, t), 8.52 (1H, d), 8.44 (1H, t), 8.09 (1H, dd), 7.77 (1H, s), 7.50 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.43 (1H, septet), 3.81 (1H, quintet), 3.69 (4H, t), 3.47-3.37 (1H, m), 3.21-3.10 (1H, m), 2.83-2.68 (2H, m), 2.40-2.24 (4H, m), 2.05-1.86 (2H, m), 1.97 (2H, quintet), 1.88 (3H, s, OAc), 1.68-1.53 (2H, m).

Example 193

7-(Aminosulfonyl)-*N*-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



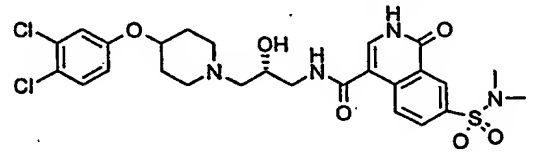
Prepared as described in Example 189 following Preparation 7 using 7-(aminosulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 569/571 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.65 (1H, s), 8.40 (1H, d), 8.39 (1H, t), 8.09 (1H, dd), 7.69 (1H, s), 7.49 (1H, d), 7.50 (2H, s), 7.25 (1H, d), 6.98 (1H, dd), 4.77 (1H, s), 4.44 (1H, septet), 3.85-3.77 (1H, m), 3.41 (1H, dt), 3.14 (1H, dt), 2.81-2.69 (2H, m), 2.41-2.25 (4H, m), 1.96-1.86 (2H, m), 1.67-1.54 (2H, m).

Example 194

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-[(dimethylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



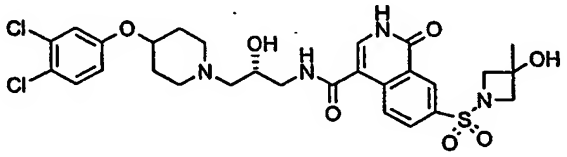
Prepared as described in Example 189 following Preparation 7 using 7-[(dimethylamino)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 597/599 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.49 (1H, s), 8.48 (1H, d), 8.43 (1H, t), 8.04 (1H, dd), 7.75 (1H, s), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.44 (1H, septet), 3.81 (1H, quintet), 3.46-3.37 (1H, m), 3.18-3.11 (1H, m), 2.82-2.69 (2H, m), 2.64 (6H, s), 2.42-2.26 (4H, m), 1.95-1.86 (2H, m), 1.89 (3H, s, OAc), 1.60 (2H, dt).

Example 195

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-[(3-hydroxy-3-methylazetidin-1-yl)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



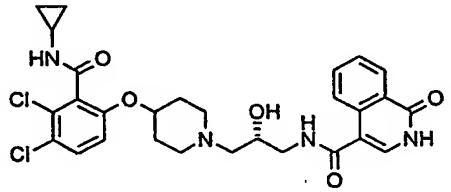
Prepared as described in Example 189 following Preparation 7 using 7-[(3-hydroxy-3-methylazetidin-1-yl)sulfonyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 639/641 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.53 (1H, d), 8.51 (1H, d), 8.45 (1H, t), 8.08 (1H, dd), 7.77 (1H, s), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.44 (1H, septet), 3.82 (1H, quintet), 3.60 (2H, d), 3.45 (2H, d), 3.45-3.40 (1H, m), 3.19-3.10 (1H, m), 2.81-2.69 (2H, m), 2.42-2.25 (4H, m), 1.96-1.84 (2H, m), 1.88 (3H, s, OAc), 1.66-1.55 (2H, m).

Example 196

N-[(2*R*)-3-(4-{3,4-Dichloro-2-[(cyclopropylamino)carbonyl]phenoxy}piperidin-1-yl)-2-hydroxypropyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



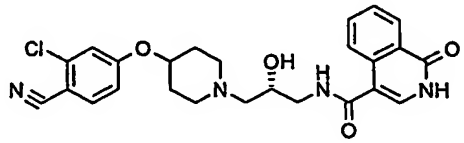
Prepared as described in Example 35 following Preparation 35 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 573/575 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, d), 8.09 (1H, d), 7.68 (1H, t), 7.49 (1H, s), 7.48 (1H, t), 7.38 (1H, d), 6.97 (1H, d), 4.54-4.48 (1H, m), 4.03-3.97 (1H, m), 3.44 (1H, dd), 3.30 (1H, dd), 2.90-2.79 (2H, m), 2.76-2.58 (5H, m), 1.98-1.89 (2H, m), 1.87-1.79 (2H, m), 1.85 (3H, s, OAc), 0.70-0.65 (2H, m), 0.52-0.48 (2H, m).

Example 197

N-{(2*R*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



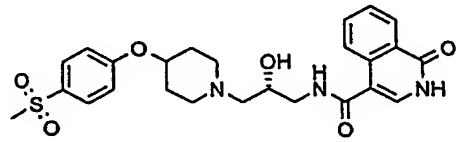
Prepared as described in Example 35 following Preparation 24 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 481 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.36 (1H, dd), 8.19 (1H, d), 7.86 (2H, d), 7.77-7.75 (2H, m), 7.57 (2H, td), 7.12 (2H, d), 4.62-4.56 (1H, m), 4.07-4.01 (1H, m), 3.57 (1H, dd), 3.38 (1H, dd), 3.08 (3H, s), 2.98-2.88 (2H, m), 2.66-2.55 (4H, m), 2.12-2.04 (2H, m), 1.92-1.83 (2H, m).

Example 198

N-((2*R*)-2-Hydroxy-3-{4-[4-(methylsulfonyl)phenoxy]piperidin-1-yl}propyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



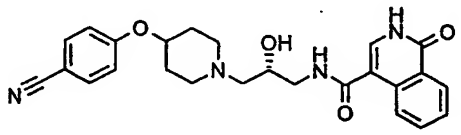
Prepared as described in Example 35 following Preparation 25 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 500 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.36 (1H, dd), 8.19 (1H, d), 7.86 (2H, d), 7.77-7.75 (2H, m), 7.57 (2H, td), 7.12 (2H, d), 4.62-4.56 (1H, m), 4.07-4.01 (1H, m), 3.57 (1H, dd), 3.38 (1H, dd), 3.08 (3H, s), 2.98-2.88 (2H, m), 2.66-2.55 (4H, m), 2.12-2.04 (2H, m), 1.92-1.83 (2H, m).

Example 199

N-{(2*R*)-3-[4-(4-Cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



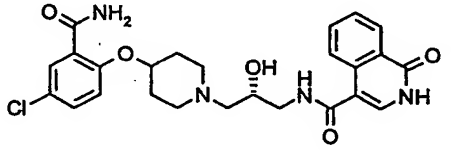
Prepared as described in Example 35 following Preparation 26 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 447 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.31 (1H, t), 8.22 (2H, d), 7.75-7.71 (3H, m), 7.54-7.50 (2H, m), 7.12 (2H, d), 4.80-4.73 (1H, m), 4.56-4.49 (1H, m), 3.83-3.77 (1H, m), 3.42-3.35 (2H, m), 3.18-3.11 (1H, m), 2.81-2.71 (2H, m), 2.41-2.27 (4H, m), 1.98-1.91 (2H, m), 1.68-1.59 (2H, m).

Example 200

N-((2*R*)-3-{4-[2-(Aminocarbonyl)-4-chlorophenoxy]piperidin-1-yl}-2-hydroxypropyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



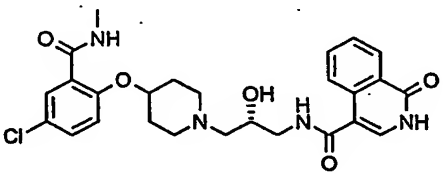
Prepared as described in Example 35 following Preparation 33 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 499 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, d), 8.08 (1H, d), 7.78 (1H, d), 7.67 (1H, td), 7.48 (1H, t), 7.47 (1H, s), 7.35 (1H, dd), 7.08 (1H, d), 4.56-4.50 (1H, m), 3.94-3.89 (1H, m), 3.46 (1H, dd), 3.27 (1H, dd), 2.79-2.70 (2H, m), 2.46-2.36 (4H, m), 2.03-1.95 (2H, m), 1.82-1.73 (2H, m).

Example 201

N-[(2*R*)-3-(4-{4-Chloro-2-[(methylamino)carbonyl]phenoxy}piperidin-1-yl)-2-hydroxypropyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



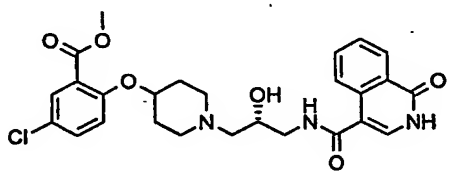
Prepared as described in Example 35 following Preparation 32 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 513 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, d), 8.09 (1H, d), 7.67 (1H, td), 7.63 (1H, d), 7.48 (1H, s), 7.48 (1H, td), 7.33 (1H, dd), 7.07 (1H, d), 4.59-4.51 (1H, m), 4.01-3.94 (1H, m), 3.46 (1H, dd), 3.28 (1H, dd), 2.91-2.80 (2H, m), 2.83 (3H, s), 2.66-2.54 (4H, m), 2.05-1.94 (2H, m), 1.90-1.79 (2H, m).

Example 202

Methyl 5-chloro-2-{[1-((2*R*)-2-hydroxy-3-{[(1-oxo-1,2-dihydroisoquinolin-4-yl)carbonyl]amino}propyl)piperidin-4-yl]oxy}benzoate acetate salt



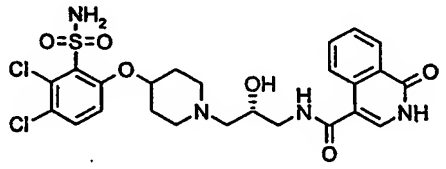
Prepared as described in Example 35 following Preparation 31 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 513 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, dd), 8.09 (1H, d), 7.67 (1H, td), 7.60 (1H, d), 7.49 (1H, s), 7.48 (1H, td), 7.38 (1H, dd), 7.06 (1H, d), 4.59-4.54 (1H, m), 4.05-3.99 (1H, m), 3.76 (3H, s), 3.45 (1H, dd), 3.30 (1H, dd), 3.03-2.92 (2H, m), 2.79-2.61 (4H, m), 2.00-1.86 (4H, m), 1.84 (3H, s, OAc).

Example 203

N-((2*R*)-3-{4-[2-(Aminosulfonyl)-3,4-dichlorophenoxy]piperidin-1-yl}-2-hydroxypropyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide trifluoroacetate salt



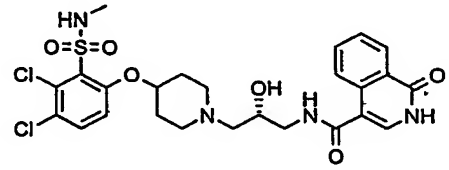
Prepared as described in Example 35 following Preparation 40 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 569/571 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.26 (1H, d), 8.09 (1H, d), 7.71 (1H, t), 7.62 (1H, d), 7.52 (1H, s), 7.48 (1H, t), 7.18 (1H, d), 5.02 (1H, s), 4.23-4.15 (1H, m), 3.55 (1H, t), 3.46-3.33 (5H, m), 3.16-3.08 (2H, m), 2.26 (2H, t), 2.15-2.00 (2H, m).

Example 204

N-[(2*R*)-3-(4-{3,4-Dichloro-2-[(methylamino)sulfonyl]phenoxy}piperidin-1-yl)-2-hydroxypropyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



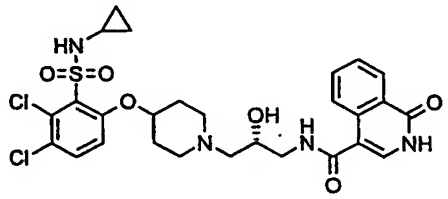
Prepared as described in Example 35 following Preparation 41 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 583/585 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, d), 8.08 (1H, d), 7.69 (1H, td), 7.60 (1H, d), 7.49 (1H, s), 7.48 (1H, td), 7.16 (1H, d), 4.73-4.68 (1H, m), 4.05-3.99 (1H, m), 3.44 (1H, dd), 3.30 (1H, dd), 3.15-3.04 (2H, m), 2.78-2.63 (4H, m), 2.52 (3H, s), 2.07-1.93 (4H, m), 1.85 (3H, s, OAc).

Example 205

N-[(2*R*)-3-(4-{3,4-Dichloro-2-[(cyclopropylamino)sulfonyl]phenoxy}piperidin-1-yl)-2-hydroxypropyl]-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



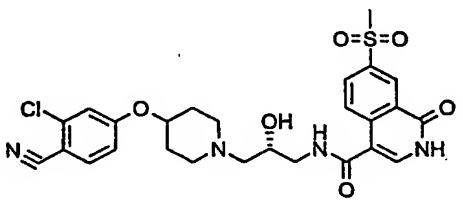
Prepared as described in Example 35 following Preparation 42 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 609/611 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.25 (1H, d), 8.08 (1H, d), 7.68 (1H, t), 7.61 (1H, d), 7.49 (1H, s), 7.47 (1H, t), 7.17 (1H, d), 4.72-4.65 (1H, m), 4.03-3.96 (1H, m), 3.44 (1H, dd), 3.30 (1H, dd), 3.11-2.99 (2H, m), 2.73-2.58 (4H, m), 2.19-2.13 (1H, m), 2.04-1.90 (4H, m), 1.83 (3H, s, OAc), 0.50-0.43 (4H, m).

Example 206

N-{(2*R*)-3-[4-(3-Chloro-4-cyanophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



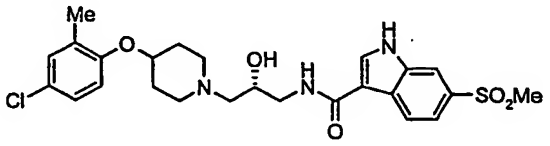
Prepared as described in Example 189 following Preparation 24 using 7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 559 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.78 (1H, d), 8.35 (1H, d), 8.14 (1H, dd), 7.68 (1H, s), 7.60 (1H, d), 7.12 (1H, d), 6.95 (1H, dd), 4.56-4.51 (1H, m), 4.01-3.95 (1H, m), 3.47 (1H, dd), 3.28 (1H, dd), 3.10 (3H, s), 2.94-2.85 (2H, m), 2.64-2.52 (4H, m), 2.04-1.95 (2H, m), 1.86 (3H, s), 1.83-1.74 (2H, m).

Example 207

N-{(2*R*)-3-{4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxy-2-methylpropyl}-6-(methylsulphonyl)-1*H*-indole-3-carboxamide



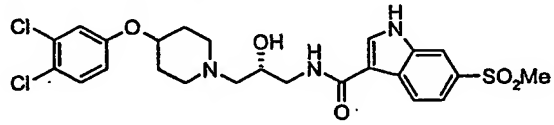
Prepared as described in Example 189 following Preparation 10 using 6-(methylsulphonyl)-1*H*-indole-3-carboxylic acid.

MS (APCI) 520/522/524 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.35 (1H, d), 8.19 (1H, s), 8.07 (1H, d), 7.69 (1H, dd), 7.11 (1H, d), 7.08 (1H, dd), 6.88 (1H, d), 4.56-4.48 (1H, m), 4.20-4.12 (1H, m), 3.57 (1H, dd), 3.43 (1H, dd), 3.19-3.12 (5H, s), 3.03-2.98 (2H, m), 2.94 (1H, dd), 2.85 (1H, m), 2.18 (3h, s), 2.16-2.08 (2H, m), 2.03-1.94 (2H, m).

Example 208

N-{(2*R*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(methylsulphonyl)-1*H*-indole-3-carboxamide



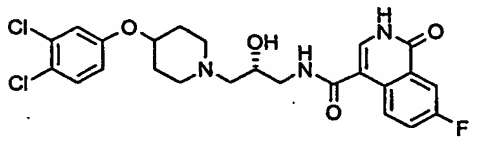
Prepared as described in Example 189 following Preparation 8 using 6-(methylsulphonyl)-1*H*-indole-3-carboxylic acid.

MS (APCI) 540/542/544 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.35 (1H, d), 8.34 (1H, s), 8.06 (1H, d), 7.69 (1H, dd), 7.38 (1H, d), 7.09 (1H, d), 6.87 (1H, dd), 4.50-4.43 (1H, m), 4.12-4.06 (1H, m), 3.57 (1H, dd), 3.41 (1H, dd), 3.13 (3H, s), 3.07-2.99 (2H, m), 2.81-2.68 (4H, m), 2.12-2.04 (2H, m), 1.94-1.82 (2H, m).

Example 209

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



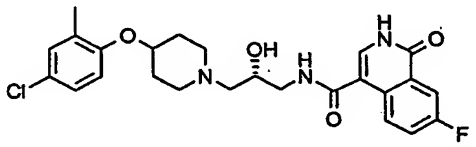
Prepared as described in Example 189 following Preparation 7 using 7-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 508/510 $(M+H)^+$

^{1}H NMR δ (DMSO) 11.73 (1H, s), 8.39-8.26 (2H, m), 7.88 (1H, dd), 7.64 (1H, td), 7.54 (1H, s), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 4.79-4.71 (1H, m), 4.48-4.38 (1H, m), 3.85-3.75 (1H, m), 3.46-3.34 (1H, m), 3.19-3.09 (1H, m), 2.82-2.65 (2H, m), 2.43-2.23 (4H, m), 1.97-1.84 (2H, m), 1.67-1.53 (2H, m).

Example 210

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



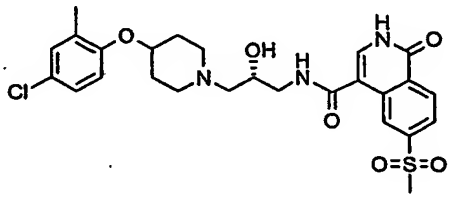
Prepared as described in Example 189 following Preparation 10 using 7-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 488 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.42-8.28 (2H, m), 7.88 (1H, dd), 7.64 (1H, td), 7.55 (1H, s), 7.20 (1H, d), 7.14 (1H, dd), 6.98 (1H, d), 4.43-4.33 (1H, m), 3.85-3.75 (1H, m), 3.45-3.34 (1H, m), 3.20-3.08 (1H, m), 2.75-2.60 (2H, m), 2.42-2.25 (4H, m), 2.14 (3H, s), 1.94-1.81 (2H, m), 1.70-1.56 (2H, m).

Example 211

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



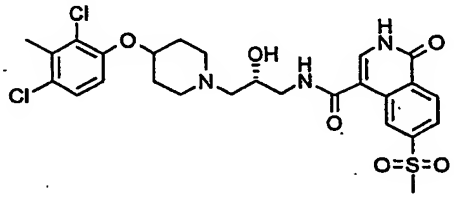
Prepared as described in Example 189 following Preparation 10 using 6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 548 $(M+H)^+$

^{1}H NMR δ (DMSO) 11.98 (1H, s), 8.89 (1H, d), 8.44 (1H, d), 8.42 (1H, t), 8.01 (1H, dd), 7.76-7.72 (1H, m), 7.20 (1H, d), 7.14 (1H, dd), 6.98 (1H, d), 4.77 (1H, d), 4.43-4.34 (1H, m), 3.86-3.77 (1H, m), 3.42 (1H, td), 3.28 (3H, s), 3.17 (1H, quintet), 2.77-2.63 (2H, m), 2.42-2.29 (4H, m), 2.14 (3H, s), 1.95-1.84 (2H, m), 1.71-1.58 (2H, m).

Example 212

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



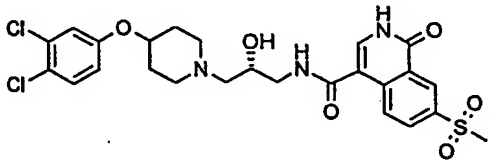
Prepared as described in Example 189 following Preparation 13 using 6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 581/583 $(M+H)^+$

^{1}H NMR δ (DMSO) 11.97 (1H, d), 8.89 (1H, d), 8.44 (1H, d), 8.42 (1H, t), 8.01 (1H, dd), 7.76-7.72 (1H, m), 7.35 (1H, d), 7.10 (1H, d), 4.80-4.73 (1H, m), 4.53-4.44 (1H, m), 3.86-3.76 (1H, m), 3.42 (1H, td), 3.28 (3H, s), 3.21-3.12 (1H, m), 2.79-2.65 (2H, m), 2.40 (3H, s), 2.42-2.30 (4H, m), 1.95-1.85 (2H, m), 1.74-1.61 (2H, m).

Example 213

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



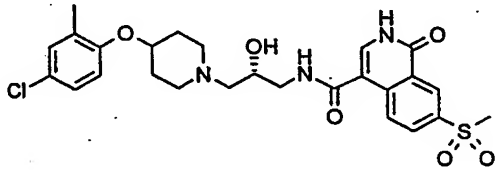
Prepared as described in Example 189 following Preparation 7 using 7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 568/566 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.70 (1H, s), 8.46 (1H, d), 8.16 (1H, dd), 8.10 (1H, t), 7.70 (1H, s), 7.45 (1H, d), 7.18 (1H, d), 6.94 (1H, dd), 4.39 (1H, septet), 3.82 (1H, quintet), 3.42 (1H, dt), 3.30-3.09 (1H, m), 3.22 (3H, s), 2.82-2.67 (2H, m), 2.45-2.27 (4H, m), 1.99-1.80 (2H, m), 1.89 (3H, s, OAc), 1.72-1.53 (2H, m).

Example 214

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



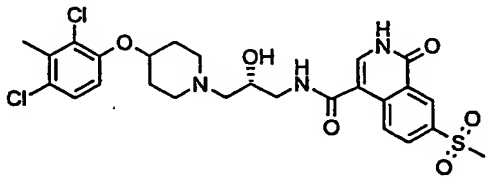
Prepared as described in Example 189 following Preparation 10 using 7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 548/550 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.68 (1H, d), 8.48 (1H, d), 8.43 (1H, t), 8.20 (1H, dd), 7.76 (1H, s), 7.21 (1H, d), 7.15 (1H, dd), 6.98 (1H, d), 4.84-4.72 (1H, m), 4.46-4.31 (1H, m), 3.88-3.74 (1H, m), 3.49-3.34 (1H, m), 3.28 (3H, s), 3.22-3.08 (1H, m), 2.78-2.60 (2H, m), 2.44-2.24 (4H, m), 2.14 (3H, s), 1.98-1.79 (2H, m), 1.74-1.54 (2H, m).

Example 215

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate salt



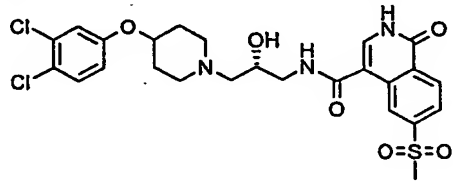
Prepared as described in Example 189 following Preparation 13 using 7-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 582/584 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.68 (1H, d), 8.47 (1H, d), 8.44 (1H, t), 8.20 (1H, dd), 7.76 (1H, s), 7.35 (1H, d), 7.10 (1H, d), 4.53-4.44 (1H, m), 3.81 (1H, quintet), 3.42 (1H, dt), 3.20-3.09 (1H, m), 2.77-2.65 (2H, m), 2.40 (3H, s), 2.39-2.28 (4H, m), 1.95-1.85 (2H, m), 1.87 (3H, s, OAc), 1.73-1.61 (2H, m).

Example 216

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide

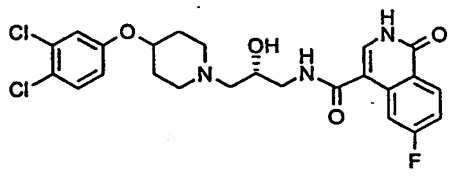


Prepared as described in Example 189 following Preparation 7 using 6-(methylsulfonyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (ESI) 568/570 $(M+H)^+$

Example 217

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



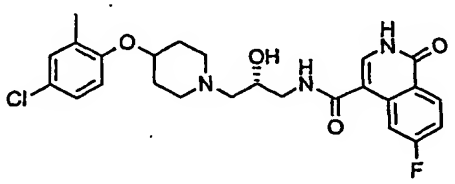
Prepared as described in Example 189 following Preparation 7 using 6-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 508/510 $(M+H)^+$

^1H NMR δ (DMSO) 11.70 (1H, d), 8.34 (1H, t), 8.28 (1H, dd), 8.03 (1H, dd), 7.64 (1H, d), 7.49 (1H, d), 7.38 (1H, td), 7.25 (1H, d), 6.98 (1H, dd), 4.80-4.70 (1H, m), 4.44 (1H, septet), 3.87-3.73 (1H, m), 3.45-3.36 (1H, m), 3.14 (1H, quintet), 2.84-2.66 (2H, m), 2.43-2.21 (4H, m), 1.99-1.84 (2H, m),1.69-1.51 (2H, m).

Example 218

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide

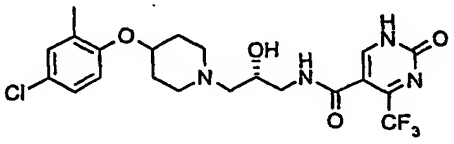


Prepared as described in Example 189 following Preparation 10 using 6-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (ESI) 488/490 $(M+H)^+$

Example 219

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyrimidine-5-carboxamide

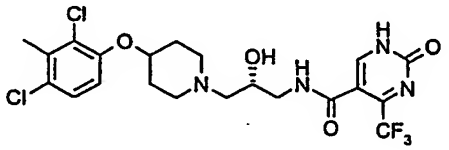


Prepared as described in Example 35 following Preparation 10 using 2-oxo-4-(trifluoromethyl)-1,2-dihydropyrimidine-5-carbonyl chloride.

MS (ESI) 489/491 $(M+H)^+$

Example 220

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyrimidine-5-carboxamide

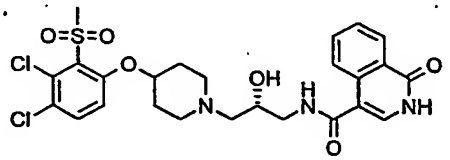


Prepared as described in Example 35 following Preparation 13 using 2-oxo-4-(trifluoromethyl)-1,2-dihydropyrimidine-5-carbonyl chloride.

MS (ESI) 523/525 $(M+H)^+$

Example 221

N-((2*R*)-3-{4-[3,4-Dichloro-2-(methylsulfonyl)phenoxy]piperidin-1-yl}-2-hydroxypropyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide acetate



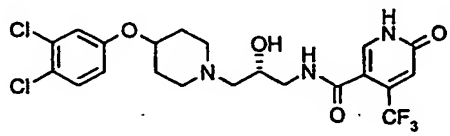
Prepared as described in Example 35 following Preparation 48 using 1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 568/570 $(M+H)^+$

^{1}H NMR δ (CD_3OD) 8.35 (1H, d), 8.18 (1H, d), 7.78 (1H, t), 7.76 (1H, d), 7.58 (1H, s), 7.57 (1H, t), 7.28 (1H, d), 4.87-4.80 (1H, m), 4.13-4.07 (1H, m), 3.54 (1H, dd), 3.40 (1H, dd), 3.35 (3H, s), 3.16-3.06 (2H, m), 2.85-2.69 (4H, m), 2.16-2.00 (4H, m), 1.94 (3H, s).

Example 222

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide acetate salt



Prepared as described in Example 35 following Preparation 7 using 6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl chloride, which was prepared by

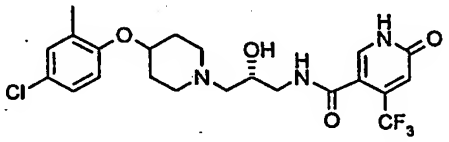
hydrolysis with sodium hydroxide followed by treatment with thionyl chloride of the commercially available 6-chloro-4-trifluoromethyl methyl nicotinoate).

MS (APCI) 508/510 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.35 (1H, t), 7.77 (1H, s), 7.49 (1H, d), 7.25 (1H, d), 6.98 (1H, dd), 6.72 (1H, s), 4.43 (1H, septet), 3.71 (1H, quintet), 3.29 (1H, dt), 3.06 (1H, dt), 2.78 - 2.66 (2H, m), 2.36-2.24 (4H, m), 1.95-1.86 (2H, m), 1.90 (3H, s), 1.65-1.54 (2H, m).

Example 223

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide acetate salt



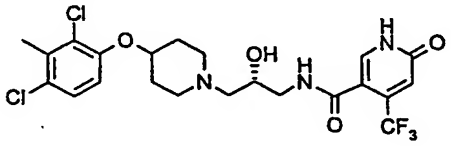
Prepared as described in Example 35 following Preparation 10 using 6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl chloride.

MS (APCI) 488/490 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.35 (1H, t), 7.77 (1H, s), 7.20 (1H, s), 7.15 (1H, dd), 6.98 (1H, d), 6.73 (1H, s), 4.42 - 4.34 (1H, m), 3.72 (1H, quintet), 3.33 - 3.27 (1H, m), 3.06 (1H, dt), 2.71 - 2.61 (2H, m), 2.37 - 2.25 (4H, m), 2.14 (3H, s), 1.93 - 1.84 (2H, m), 1.91 (3H, s), 1.69 - 1.58 (2H, m).

Example 224

N-{(2*R*)-3-[4-(2,4-Dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide



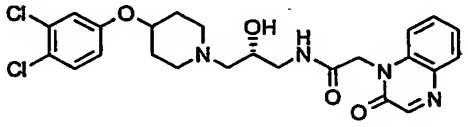
Prepared as described in Example 35 following Preparation 13 using 6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl chloride.

MS (APCI) 522/524 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.32 (1H, t), 7.79 (1H, s), 7.35 (1H, d), 7.10 (1H, d), 6.69 (1H, s), 4.49 (1H, septet), 3.72 (1H, quintet), 3.30 (1H, dt), 3.07 (1H, dt), 2.74 - 2.64 (2H, m), 2.40 (3H, s), 2.37 - 2.25 (4H, m), 1.94 - 1.84 (2H, m), 1.89 (3H, s), 1.71 - 1.61 (2H, m).

Example 225

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-(2-oxoquinoxalin-1(2*H*)-yl)acetamide



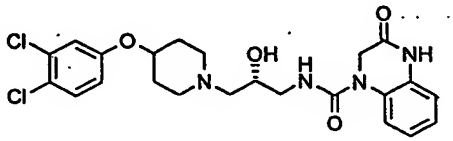
Prepared as described in Example 1 following Preparation 7 using (2-oxoquinoxalin-1-(2*H*)-yl)acetic acid.

MS (APCI) 505/507 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.37 (1H, s), 7.92 (1H, d), 7.61 (1H, t), 7.49 (1H, d), 7.40 (1H, t), 7.32 (1H, d), 6.99 (1H, d), 6.74 (1H, dd), 6.72 (1H, bd s), 4.91 (2H, m), 4.36-4.26 (1H, m), 3.86-3.76 (1H, m), 3.52-3.42 (1H, m), 3.26-3.18 (1H, m), 2.88-2.80 (1H, m), 2.63-2.53 (2H, m), 2.40-2.26 (3H, m), 2.06-1.92 (2H, m), 1.87-1.73 (2H, m).

Example 226

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-oxo-3,4-dihydroquinoxaline-1(2*H*)-carboxamide



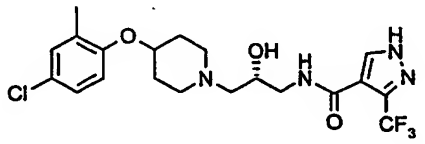
Prepared as described in Example 35 following Preparation 7 using 3-oxo-3,4-dihydroquinoxaline-1(2*H*)-carbonyl chloride.

MS (APCI) 505/507 $(M+H)^+$

^{1}H NMR δ ($CDCl_3$) 8.26 (1H, s), 7.43 (1H, d), 7.31 (1H, d), 7.19-7.09 (1H, m), 6.99 (1H, d), 6.94 (1H, d), 6.75 (1H, dd), 5.72 (1H, t), 4.44 (2H, s), 4.30-4.22 (1H, m), 3.88-3.81 (1H, m), 3.58-3.52 (1H, m), 3.17-3.11 (1H, m), 2.93-2.85 (1H, m), 2.67-2.61 (1H, m), 2.57-2.53 (1H, m), 2.44-2.40 (1H, m), 2.36-2.29 (2H, m), 2.00-1.90 (2H, m), 1.80-1.70 (2H, m).

Example 227

N-{(2*R*)-3-[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide



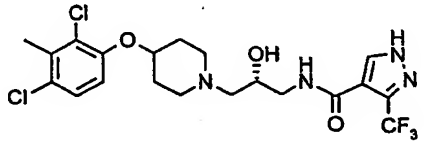
Prepared as described in Example 1 following Preparation 10 using 3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid.

MS (APCI) 460/462 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.41 (1H, s), 8.15 (1H, t), 7.20 (1H, d), 7.14 (1H, dd), 6.98 (1H, d), 4.42-4.36 (1H, m), 3.77-3.71 (1H, m), 3.39-3.33 (1H, m), 3.10-3.04 (1H, m), 2.73-2.63 (2H, m), 2.36-2.26 (4H, m), 2.14 (3H, s), 1.92-1.82 (2H, m), 1.70-1.60 (2H, m).

Example 228

N-{(2*R*)-3-[4-(2,4-dichloro-3-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide



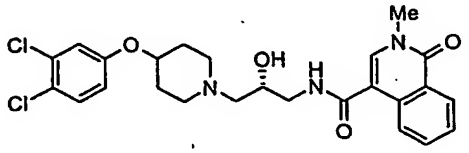
Prepared as described in Example 1 following Preparation 13 using using 3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid.

MS (APCI) 495/497 $(M+H)^+$

^{1}H NMR δ (DMSO) 8.41 (1H, s), 8.15 (1H, t), 7.34 (1H, d), 7.09 (1H, dd), 4.50-4.42 (1H, m), 3.77-3.71 (1H, m), 3.37-3.33 (1H, m), 3.10-3.04 (1H, m), 2.74-2.64 (2H, m), 2.39 (3H, s), 2.36-2.26 (4H, m), 1.96-1.86 (2H, m), 1.69-1.62 (2H, m).

Example 229

N-{(2*R*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl}-2-hydroxypropyl}-1-oxo-1,2-dihydro-2-methylisoquinoline-4-carboxamide



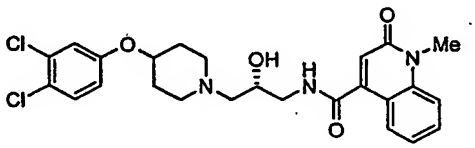
Prepared as described in Example 1 following Preparation 7 using 2-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid.

MS (APCI) 504/506/508 $(M+H)^+$

^1H NMR δ ($CDCl_3$) 8.47 (1H, d), 8.14 (1H, d), 7.70 (1H, t), 7.61 (1H, s), 7.53 (1H, t), 7.33 (1H, d), 7.00 (1H, d), 6.76 (1H, dd), 6.58 (1H, bd t), 4.42-4.32 (1H, m), 4.06-3.96 (1H, m), 3.80-3.70 (1H, m), 3.63 (3H, s), 3.44-3.34 (1H, m), 3.02-2.92 (1H, m), 2.78-2.68 (2H, m), 2.59- 2.45 (3H, m), 2.16-2.00 (2H, m), 1.96-1.80 (2H, m).

Example 230

N-{(2*R*)-3-{4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-1,2-dihydro-1-methylquinoline-4-carboxamide



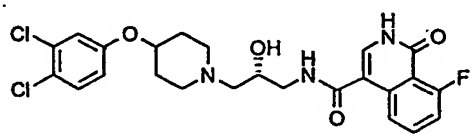
Prepared as described in Example 1 following Preparation 7 using 1-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylic acid.

MS (APCI) m/z 504/506/508 $(M+H)^+$

^1H NMR δ ($CDCl_3$) 7.97 (1H, d), 7.62 (1H, t), 7.40 (1H, d), 7.32 (1H, d), 7.28 (1H, t), 7.00 (1H, d), 6.83 (1H, s), 6.76 (1H, dd), 6.72 (1H, t), 4.39-4.31 (1H, m), 4.04-3.94 (1H, m), 3.78-3.70 (1H, m), 3.72 (3H, s), 3.47-3.37 (1H, m), 3.00-2.90 (1H, m), 2.75-2.67 (2H, m), 2.56-2.42 (3H, m), 2.10-1.94 (2H, m), 1.94-1.78 (2H, m).

Example 231

N-{(2*R*)-3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-8-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide

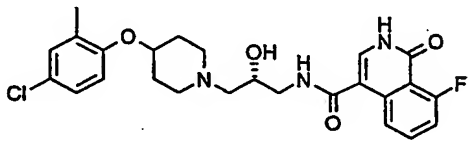


Prepared as described in Example 35 following Preparation 7 using 8-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 508/510 $(M+H)^+$

Example 232

N-{(2*R*)-3-[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]-2-hydroxypropyl}-8-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide

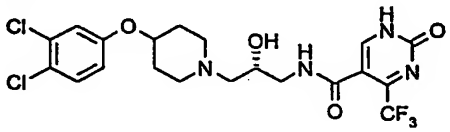


Prepared as described in Example 35 following Preparation 10 using 8-fluoro-1-oxo-1,2-dihydroisoquinoline-4-carbonyl chloride.

MS (APCI) 488/490 $(M+H)^+$

Example 233

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyrimidine-5-carboxamide

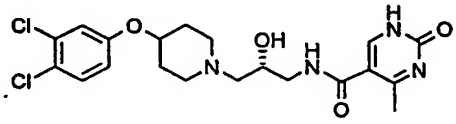


Prepared as described in Example 35 following Preparation 7 using 2-oxo-4-(trifluoromethyl)-1,2-dihydropyrimidine-5-carbonyl chloride.

MS (EPCI) 509/511 $(M+H)^+$

Example 234

N-{(2*R*)-3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]-2-hydroxypropyl}-4-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxamide



Prepared as described in Example 35 following Preparation 7 using 4-methyl-2-oxo-1,2-dihydropyrimidine-5-carbonyl chloride.

MS (EPCI) 455/457 $(M+H)^+$

Example 235

Pharmacological Analysis: Calcium flux $[Ca^{2+}]_i$ assay

Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ ml^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for twoh) at 25μl/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} = 490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

Compounds of the Examples were found to be antagonists if the increase in fluorescence induced by eotaxin (a selective CCR3 agonist) was inhibited in a concentration dependent manner. The concentration of antagonist required to inhibit the fluorescence by 50% can be used to determine the IC_{50} for the antagonist at the CCR3 receptor.

Example 236

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ ml^{-1} in RPMI containing 200 IU/ml penicillin, 200 μg/ml streptomycin sulfate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis

plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin 0.1 to 100nM (a selective CCR3 agonist over this concentration range) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 μl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Compounds of the Examples were found to be antagonists of eotaxin mediated human eosinophil chemotaxis if the concentration response to eotaxin was shifted to the right of the control curve. Measuring the concentration of eotaxin required to give 50% chemotaxis in the presence or absence of compounds enables the apparent affinity of the compounds at CCR3 to be calculated, or the assay can be used to determine activity of compounds at a set concentration of compound against a predifined concentration of eotaxin.

Example	% inhibition at 3nM eotaxin (1uM compound)
10	106
17	103
45	102
46	105
47	104
52	95

53	105
58	104
132	101
186	104
192	103
197	103
206	99
212	103
215	103
227	103

Example 237

Guinea-pig isolated trachea

(See for example, Harrison, R.W.S., Carswell, H. & Young, J.M. (1984) European J. Pharmacol., 106, 405-409.)

Male albino Dunkin-Hartley guinea-pigs (250g) were killed by cervical dislocation and the whole trachea removed. After clearing the adherent connective tissue, the trachea was cut into six ring segments each three cartilage bands wide and then suspended in 20ml organ baths containing Krebs-Henseleit solution of the following composition (mM): NaCl 117.6, NaH_2PO_4 0.9, $NaHCO_3$ 25.0, $MgSO_4$ 1.2, KCl 5.4, $CaCl_2$ 2.6 and glucose 11.1. The buffer was maintained at 37°C and gassed with 5% CO_2 in oxygen. Indomethacin (2.8μM) was added to the Krebs solution to prevent development of smooth muscle tone due to the synthesis of cyclo-oxygenase products. The tracheal rings were suspended between two parallel tungsten wire hooks, one attached to an Ormed beam isometric force transducer and the other to a stationary support in the organ bath. Changes in isometric force were recorded on 2-channel Sekonic flat bed chart recorders.

Experimental protocols

At the beginning of each experiment a force of 1g was applied to the tissues and this was reinstated over a 60 minute equilibration period until a steady resting tone was achieved. Subsequently, a cumulative histamine concentration effect (E/[A]) curve was constructed at 0.5 $\log_{10}$ unit increments, in each tissue. The tissues were then washed and approximately 30 minutes later, test compound or vehicle (20% DMSO) was added.

Following an incubation period of 60 minutes a second E/[A] curve was performed to histamine.

Contraction responses were recorded as a percentage of the first curve maximum.

Data analysis

Experimental E/[A] curve data were analysed for the purposes of estimating the potencies ($p[A_{50}]$ values) of histamine in the absence and presence of the test compound. Affinity (pA_2) values of test compounds were subsequently calculated using the following equation:

$$\log(r-1) = \log[B] + pA_2$$

where $r = [A]_{50}$ in presence of test compound/$[A]_{50}$ in absence of antagonist and [B] is the concentration of test compound. Compounds of the Examples were found to be H1 antagonists.

Example 238

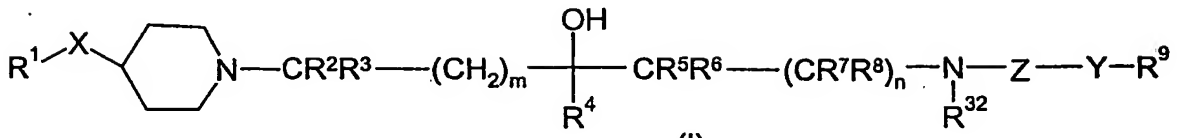
Histamine H1 receptor binding activity of compounds of the invention was assessed by competition displacement of 1nM [3H]-pyrilamine (Amersham, Bucks, Product code TRK 608, specific activity 30Ci/mmol) to 2μg membranes prepared from recombinant CHO-K1 cells expressing the human H1 receptor (Euroscreen SA, Brussels, Belgium, product code ES-390-M) in assay buffer (50mM Tris pH 7.4 containing 2mM $MgCl_2$, 250mM sucrose and 100mM NaCl) for 1 hour at room temperature.

Example	H1 pKi /[1328_S]
10	8.4
17	8.1
45	7.7
46	8.2
47	8.1
52	8.4
53	8.1
58	7.2
132	6.6
186	7.9

192	8.7
197	6.8
206	6.6
212	7.8
215	7.3
227	7.6

CLAIMS

1. A compound of formula (I):



(I)

wherein:

X is CH_2, O, $S(O)_2$ or NR^{10};

Y is a bond, CH_2, NR^{35}, CH_2NH, $CH_2NHC(O)$, $CH(OH)$, $CH(NHC(O)R^{33})$, $CH(NHS(O)_2R^{34})$, CH_2O or CH_2S;

Z is C(O), or when Y is a bond Z can also be $S(O)_2$;

R^1 is optionally substituted aryl, optionally substituted heterocyclyl or C_{4-6} cycloalkyl fused to a benzene ring;

R^4 is hydrogen, C_{1-6} alkyl (optionally substituted by C_{3-6} cycloalkyl) or C_{3-6} cycloalkyl;

R^2, R^3, R^5, R^6, R^7 and R^8 are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

m and n are, independently, 0 or 1;

R^9 is optionally substituted aryl or optionally substituted heterocyclyl;

R^{10}, R^{32} and R^{35} are, independently, hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^{33} and R^{34} are C_{1-6} alkyl or C_{3-6} cycloalkyl;

wherein the foregoing aryl and heterocyclyl moieties are, where possible, optionally substituted by: halogen, cyano, nitro, hydroxy, oxo, $S(O)_kR^{12}$, $OC(O)NR^{13}R^{14}$, $NR^{15}R^{16}$, $NR^{17}C(O)R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, $S(O)_2NR^{22}R^{23}$, $NR^{24}S(O)_2R^{25}$, $C(O)NR^{26}R^{27}$, $C(O)R^{28}$, CO_2R^{29}, $NR^{30}CO_2R^{31}$, C_{1-6} alkyl (itself optionally mono-substituted by NHC(O)phenyl), C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{1-6} alkylthio, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, morpholinyl, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halogen, hydroxy, nitro, $S(O)_r(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl),

CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

k and r are, independently, 0, 1 or 2;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27}, R^{29} and R^{30} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), C_{3-6} cycloalkyl, phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

alternatively $NR^{13}R^{14}$, $NR^{15}R^{16}$, $NR^{20}R^{21}$, $NR^{22}R^{23}$, $NR^{26}R^{27}$, may, independently, form a 4-7 membered heterocyclic ring selected from the group: azetidine (itself optionally substituted by hydroxy or C_{1-4} alkyl), pyrrolidine, piperidine, azepine, 1,4-morpholine or 1,4-piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen;

R^{12}, R^{25}, R^{28} and R^{31} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as

described for R^{13} and R^{14} above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^{13} and R^{14} above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

provided that when X is CH_2 and m and n are both 0 then Y is not NR^{35};

or an N-oxide thereof; or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

2. A compound as claimed in claim 1 wherein: X is O; Y is a bond, CH_2, NR^{35}, CH_2NH, CH(OH), $CH(NHC(O)R^{33})$, $CH(NHS(O)_2R^{34})$ or CH_2O; Z is C(O), or when Y is a bond Z can also be $S(O)_2$; R^1 is optionally substituted phenyl; R^4 is hydrogen or C_{1-6} alkyl; R^2, R^3, R^5, R^6, R^7 and R^8 are, when present, all hydrogen; m and n are, independently, 0 or 1; R^9 is optionally substituted aryl or optionally substituted heterocyclyl; R^{32} and R^{35} are, independently, hydrogen or C_{1-6} alkyl; R^{33} and R^{34} are C_{1-6} alkyl; wherein the foregoing phenyl, aryl and heterocyclyl moieties are, where possible, optionally substituted by: halogen, cyano, hydroxy, oxo, $S(O)_2R^{12}$, $NR^{15}R^{16}$, $NR^{17}C(O)R^{18}$, $S(O)_2NR^{22}R^{23}$, $NR^{24}S(O)_2R^{25}$, $C(O)NR^{26}R^{27}$, CO_2R^{29}, C_{1-6} alkyl (itself optionally mono-substituted by NHC(O)phenyl), CF_3, phenyl or heteroaryl;wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3; R^{15}, R^{16}, R^{17}, R^{18}, R^{22}, R^{23}, R^{24}, R^{26}, R^{27} and R^{29} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy) or C_{3-6} cycloalkyl; alternatively $NR^{22}R^{23}$ may form an azetidine ring (itself optionally substituted by hydroxy or C_{1-4} alkyl); R^{12} and R^{25} are, independently, C_{1-6} alkyl or phenyl; or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in claim 1 or 2 wherein R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2NH(C_{3-6}$ cycloalkyl), $C(O)_2(C_{1-4}$ alkyl), $C(O)NH(C_{1-4}$ alkyl) or $C(O)NH_2$.

4. A compound as claimed in claim 1 or 3 wherein X is O.

5. A compound as claimed in claim 1, 2, 3 or 4 wherein Y is a bond.

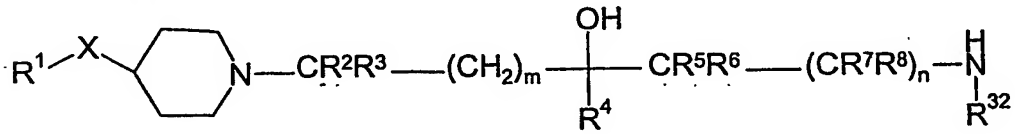
6. A compound as claimed in claim 1, 2, 3, 4 or 5 wherein Z is C(O).

7. A compound as claimed in any of the preceding claims wherein m and n are both 0.

8. A compound as claimed in any of the preceding claims wherein R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are, when present, all hydrogen.

9. A compound as claimed in any of the preceding claims wherein R^9 is optionally substituted heterocyclyl; wherein the heterocyclyl group is: thienyl, pyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,5-oxadiazolyl, pyridinyl, 1,6-dihydropyridinyl, pyrimidinyl, indolyl, indazolyl, 2,3-dihydro-1H-indazolyl, an imidazopyridinyl, 2,1,3-benzothiadiazolyl, quinoxalinyl, quinolinyl, 1,2-dihydroquinolinyl, 1,4-dihydroquinoline, isoquinolinyl, 1,2-dihydroisoquinolinyl, cinnolinyl, 3,4-dihydrophthalazinyl, 2,3-dihydro-4H-1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 1,3-dihydro-2H-isoindolyl, pyrazolotriazinyl, pyrazolopyrimidinyl, imidazobenzothiazolyl, imidazopyrimidinyl, or 2,1,3-benzoxadiazolyl, 1,3-benzothiazole, 2,3-dihydro-1,3-benzothiazole, 4,5,6,7-tetrahydroindazole or 2,3-dihydro-1H-benzimidazole; wherein the heterocyclyl is unsubstituted or substituted by one or more of: oxo (where possible), halogen, C_{1-4} alkyl, CF_3, C_{1-4} alkoxy, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ or OCF_3.

10. A process for preparing a compound as claimed in claim 1, the process comprising reacting a compound of formula (II):



(II)

wherein X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{32}, m and n are as defined above, with:

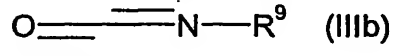
(i) when Y is a bond, CH_2, NR^{35}, CH_2NH, $CH_2NHC(O)$, CH(OH), $CH(NHCOR^{33})$, $CH(NHSO_2R^{34})$, CH_2O or CH_2S, Z is C(O), R^{35} is not

hydrogen and, R^{33} and R^{34} are as defined above, a compound of formula (IIIa):

$$L^1—CO—Y—R^9 \quad (IIIa)$$

wherein R^9 is as defined above and L^1 is a leaving group in the presence of a base, optionally in the presence of a coupling agent;

(ii) when Y is NH and Z is C(O), a compound of formula (IIIb):



(IIIb)

wherein R^9 is as defined above; or,

(iii) when Y is a bond and Z is $S(O)_2$, a compound of formula (IIIc):

$$L^1—S(O)_2—R^9 \quad (IIIc)$$

wherein R^9 is as defined above and L^1 is a leaving group in the presence of a base.

11. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof, as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier therefor.

12. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof, as claimed in claim 1, for use in therapy.

13. A compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof. as claimed in claim 1, in the manufacture of a medicament for use in therapy.

14. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof, as claimed in claim 1.

15. A process for preparing 4-(3,4-dichlorophenoxy)piperidine comprising the steps of:

a. reacting 4-hydroxypiperidine with a suitable base in a suitable solvent at room temperature; and,

b. heating the mixture so produced and 1,2-dichloro-4-fluorobenzene at a temperature in the range 50-90°C, or at reflux of the solvent used.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00258

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/52, C07D 211/14, C07D 401/12, C07D 409/12, C07D 417/12, A61K 31/445, A61K 31/4523, A61P 11/06, A61P 19/02, A61P 31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0035453 A1 (DU PONT PHARMACEUTICALS COMPANY), 22 June 2000 (22.06.00), table 1, structure f-g. compound 159,160, table 4, structure 24-35, table 7, structure 24-35 --	1-3,6-8, 11-13
X	WO 0035451 A1 (DU PONT PHARMACEUTICALS COMPANY), 22 June 2000 (22.06.00), table 1, structure f-g, compound 159,160, table 4, structure 24-35, table 7, structure 24-35 --	1-3,6-8, 11-13
X	WO 0035449 A1 (DU PONT PHARMACEUTICALS COMPANY), 22 June 2000 (22.06.00), table 1, structure f-g, compound 159,160, table 4, structure 24-35, table 7, structure 24-35 --	1-3,6-8, 11-13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 July 2003	09 -07- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer EVA JOHANSSON/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00258

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0162729 A1 (ASTRAZENECA AB), 30 August 2001 (30.08.01)	1-14
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X	WO 0058305 A1 (ASTRAZENECA AB), 5 October 2000 (05.10.00)	1-14
A	see part. example 1 (i), (ii)	15
	--	
X	WO 0162728 A1 (ASTRAZENECA AB), 30 August 2001 (30.08.01)	1-14
	--	
X	EP 0903349 A2 (F. HOFFMANN-LA ROCHE AG), 24 March 1999 (24.03.99)	1-14
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A	WO 0102381 A1 (ASTRAZENECA UK LIMITED), 11 January 2001 (11.01.01)	1-14
	--	
A	WO 0029377 A1 (F. HOFFMANN-LA ROCHE AG), 25 May 2000 (25.05.00)	1-14
	--	
A	WO 0177101 A1 (ASTRAZENECA AB), 18 October 2001 (18.10.01), see part. example 1 step a,b	15
	--	
A	WO 0012478 A1 (ZENECA LIMITED), 9 March 2000 (09.03.00), see part. page 52, lines 7-26	15
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INTERNATIONAL SEARCH REPORT

In plication No.
PCT/SE03/00258

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00258

Box I.2
Claim 14 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

Box II

Lack of unity

The International Search Authority considers that there are 2 inventions covered by the claims indicated as follows:

I: Claims 1-14 directed to novel piperidine derivatives which can be used as chemokines
II: Claim 15 directed to a process for preparing an intermediate.

The present application has been considered to contain 2 inventions which are not linked such that they form a single, general inventive concept, as required by Rules 13.1, 13.2 and 13.3 PCT for the following reasons:

Invention I relates to the problem of novel chemokines. This problem appears to be solved by novel piperidine derivatives comprising a specific substitution in 1-position.

Invention II relates to the problem of preparing an intermediate. This problem is solved by a special process for preparing 4-(3, 4-dichlorophenoxy)piperidine.

In order to fulfil the requirements of unity of invention, it is necessary that the intermediate compounds are closely interconnected with the end products. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate compound. However, the present application lacks a single general inventive concept based on the above principle. This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept. The only common structural part is a piperidine group.

As both problems and solutions are technically so different, no single general concept can be formulated based on the technical features of the inventions. Consequently, the requirements of Rule 13.1 PCT are not met.

The two groups of inventions are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00258

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		AU 2482100 A	03/07/00
		AU 3126600 A	03/07/00
		AU 3126700 A	03/07/00
		AU 4820699 A	01/02/00
		BR 9911920 A	27/03/01
		BR 9917038 A	02/04/02
		CA 2336735 A	20/01/00
		CA 2346933 A	22/06/00
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		SE 1099266 T3	
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00258

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		NO 20012977 A	20/08/01
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00258

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 2057200 A	03/07/00
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